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Edited by David B. Paintin

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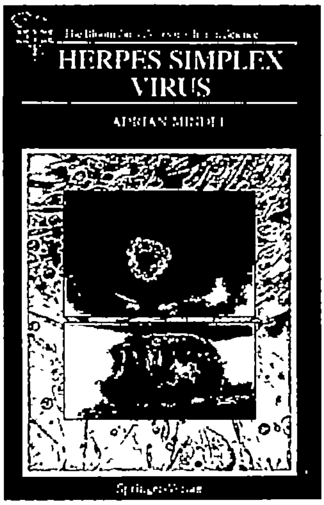

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COMMENTARIES

Obstetric and paediatric collaboration to reduce morbidity after preterm birth

In this issue of the journal (p. 11) Dr Crowley and her colleagues conclude from the results of a meta-analysis of all published reports of adequately controlled trials of antepartum corticosteroids for preventing respiratory distress syndrome (RDS) that, with the exception of certain very specific circumstances, no further placebo-controlled trials are necessary. The implication of their conclusion is that for most circumstances, the benefits of treatment are established beyond doubt, and that potential risks, both short term and long term, have been sufficiently explored to have confidence in a favourable risk/benefit ratio. In the face of this conclusion, the continued reluctance of many centres to adopt antepartum corticosteroid treatment may seem perverse, particularly when obstetricians and neonatologists so readily practice unproven forms of treatment given the blessing of 'common usage'.

Obstetricians and neonatologists probably differ in their reasons for reluctance to adopt steroids. Neonatologists have every reason to be proud of the advances in intensive care that have reduced dramatically the mortality associated with RDS. Infants of very low birthweight, who now make up so much of the load on the staff and facilities of intensive care nurseries and who yield the bulk of neonatal mortality and major morbidity, are often believed to derive no benefit from corticosteroid treatment. The analysis by Crowley and her colleagues shows this view to be incorrect. Nevertheless, some neonatologists feel that antepartum corticosteroids give least help when it is most needed, particularly as the other beneficial effects of corticosteroids in preventing intraventricular haemorrhage, necrotizing enterocolitis and patent ductus arteriosus, have yet to be shown to apply to infants of very low birthweight. Another factor that may influence the attitude of neonatologists is the prospect that surfactant replacement may lessen the need for antepartum acceleration of lung maturation. This possibility is considered further below.

The obstetrician, on the other hand, tends to give weight to the other side of the coin—the mother in active preterm labour who suffers the side-effects and potential risks of combined tocolytic and corticosteroid treatment. The obstetrician may also be concerned that delaying delivery may harm the fetus. Although results from the controlled trials are reassuring in suggesting that corticosteroid treatment, *per se*, is not associated with a statistically significant increase in the frequency of stillbirth or fetal infection, the trials were not designed to assess the risk of tocolytic treatment, since this tended to be used with equal frequency in the treatment and control groups. Reluctance to use corticosteroids based on reservations about the safety of tocolytics can be respected, but not the practice of some centres in which tocolytics are used and corticosteroids withheld. Equally irrational is the argument that corticosteroids should not be given before elective preterm caesarean section. Although it is true that none of the complications of pregnancy requiring elective preterm delivery comprise sufficiently large subgroups in any of the published controlled studies to prove or disprove efficacy, it is equally true, not only that there is no *a priori* reason for believing that corticosteroids are ineffective in such circumstances, but also that the occurence of RDS may be increased by elective section (Usher *et al.* 1971). Indeed, the risk/benefit ratio favours corticosteroid treatment most clearly before elective delivery since the risks (diabetes excepted) are minimal. Similar considerations apply when preterm labour is correctly predicted, and the necessary period of fetal exposure to corticosteroid is achieved without recourse to tocolytics.

Progress in the prevention of preterm labour has been disappointing (Papiernik *et al.* 1985). Despite this, the workload devoted to preterm delivery and care of the preterm infant has increased enormously as the result of the advances in neonatal care that have led to realistic expectations for survival of infants with birthweights as low as 600 g. As a consequence, the obstetrician has come under pressure to provide the best possible care in labour for pregnancies that previously tended to be 'written off', and the neonatologist is obliged to undertake long periods of artificial ventilation and the management of the various forms of morbidity arising out of extreme immaturity. It is hardly surprising that there is renewed enthusiasm for finding methods of preventing preterm labour and its consequences. In the absence of signs of real progress in preventing preterm births, this means, to the obstetrician, that more should be done to prepare the fetus for extrauterine life, and to the neonatologist, that the organs most affected by immaturity, the lungs, need more support than can be provided by a ventilator. In essence, the obstetric and neonatal goals may seem to be the same, in that the aim is to achieve a greater amount of intra-alveolar surfactant, either by stimulating surfactant secretion before birth or instilling surfactant after birth. The efforts of obstetricians and neonatologists to promote lung maturation should not be in competition; their combined efforts will be needed to attain better results.

Until recently, the prevailing view has been that the effects of hormones on fetal lung maturation are expressed predominantly through pulmonary surfactant and that only two hormones are involved, namely cortisol which stimulates the synthesis of surfactant, and adrenaline which stimulates its secretion. Recent research in animals shows the system to be much more complex than originally envisaged. The maturational responses to hormones are now known to include the structural components of the lungs, particularly the connective tissue elements (Schellenberg *et al.* 1987; Seidner *et al.* 1988), as well as the enzymes and substrates for the synthesis of the lipid and protein components of surfactant (Van Golde *et al.* 1988; Odom *et al.* 1988). Indeed, evidence from experiments in primates (Mitzner *et al.* 1979 and other species (Liggins *et al.* 1985; ElKady & Jobe 1987) suggests that the major effect of corticosteroids is on lung structure. Furthermore, it is clear that the full potential for accelerating lung maturation is likely to be expressed only by exploiting the synergism of a number of hormones including cortisol, triiodothyronine and prolactin (Schellenberg *et al.* 1988). Neither of the latter hormones crosses the human placenta in significant amounts, thus ruling out the possibility of therapeutic application by maternal administration. Fortunately, thyrotrophin-releasing hormone (TRH), a small peptide that readily penetrates the placenta, stimulates the secretion of both triiodothyronine and prolactin in the fetus; the response to cortisol and TRH in fetal sheep replicates that to cortisol, triiodothyronine and prolactin (Liggins *et al.* 1988*b*). Preliminary reports of clinical trials of combined treatment with betamethasone and TRH (Liggins *et al.* 1988*a*; Morales *et al.* 1989) show promise of further reducing neonatal morbidity.

Finally, an exciting observation by Ikegami *et al.* (1987), showing that the effects of corticosteroid/TRH and instillation of surfactant on pulmonary mechanics are additive, may be a pointer in the right direction. The hopes that surfactant instillation alone might prevent most cases of severe RDS have been tempered by experience (see Jobe & Ikegami 1987 for review). Does the future lie in the truly perinatal approach of preparing the lungs before birth for surfactant treatment after birth?

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Modern treatment of menorrhagia

As the pathophysiology of menorrhagia is poorly understood, management tends to be unsatisfactory and in need of improvement. Recent technical developments in hysteroscopic diagnosis and treatment have improved diagnosis, and selective endometrial destruction has refined treatment. But how effective and how safe are these new techniques? Is hysterectomy for menorrhagia to be the next major operation to fall to the cause of 'minimally invasive surgery'?

Most patients with menorrhagia have no significant uterine abnormality. Medical treatment of these women with dysfunctional bleeding often seems empirical and unhelpful, and failure of such therapy, for whatever reason, is usually considered sufficient indication for hysterectomy.

How good is medical therapy? Assessment of treatment requires the use of objective criteria; the woman's interpretation of her blood loss is insufficient (Fraser *et al.* 1984), and menorrhagia must be defined in terms of measured menstrual blood loss (Hallberg *et al.* 1966). Many medications effectively diminish blood loss, but symptoms usually return after therapy is stopped. Long-term treatment is often necessary, but this is restricted by potential side-effects associated with some agents, this problem being least when medication is used only during menstruation.

Non-steroidal anti-inflammatory drugs (NSAIDs) will decrease menstrual blood loss by an average of 30% when given to women who complain of heavy periods (Fraser 1985). Endometrial prostaglandins are elevated when menstruation is excessive (Willman *et al.* 1976). In addition, the ratio of prostaglandins E_2 to F_2 (PGE_2/PGF_2) (Smith *et al.* 1981) and the ratio of prostacyclin to thromboxane (Makarainen & Yikorkala (1986) are raised, leading to deranged haemostasis. Although production of these substances is mainly within the endometrium, many of their effects take place in the myometrium. Successful treatment with NSAIDs is associated with a fall in endometrial prostaglandin levels (Fraser 1983) and in women with menstrual blood loss in excess of 80 ml, the monthly loss is virtually halved (Hall *et al* 1987).

Ethamsylate (Harrison & Campbell 1976) and tranexamic acid (Nilsson & Rybo 1971) also decrease blood loss by 50% in women with excessive menstrual loss (>80 ml), although long-term use of the latter agent is restricted by the risk of inducing thrombosis and by a high frequency of non-specific side-effects. The mode of action of these medications is not so clear. Coagulation and fibrinolytic activity may be deranged with menorrhagia, but no clear difference in the activity of these systems has been found between women with normal and those with excesive (>80 ml) measured menstrual blood loss (Rees *et al.* 1985).

How beneficial is hormonal treatment? Women with excessive, but regular, menstruation have normal cyclical changes in oestrogen and progesterone and the majority ovulate regularly (Haynes *et al.* 1979) There are no clinical trials indicating that treatment with progesterones in the luteal phase significantly diminishes menstrual loss, but there is sound evidence that both the combined contraceptive pill (Nilsson & Rybo 1971) and danazol (Fraser 1985) are effective.

What then is the place of medical treatment? In general, NSAIDs and ethamsylate form the first line of therapy in women of all ages, and hormonal treatment is only introduced if these measures fail. The pill can be used as first-line treatment in the younger woman who also requires contraception and may be preferable in the older woman when the long-term risks may be smaller than those associated with high doses of unopposed progesterones. The long-term risk from these preparations is higher in women who smoke. Danazol has significant side-effects regardless of age and its long-term use requires caution.

Medical treatment can reduce excessive blood loss (>80 ml) by 50%. However, as only 38% of women referred for specialist care with a convincing history of excessive blood loss actually lose >80 ml/menstruation (Fraser *et al.* 1984), the effectiveness of therapy in routine clinical practice is significantly reduced. Therefore, if the clinical diagnosis of menorrhagia is based on subjective assessment, failure of medical therapy should prompt the clinician to question his initial diagnosis rather than to consider surgery

What is the place of surgery in the management of menorrhagia? Hysterectomy is still advisable if excessive menorrhagia is unresponsive to, or unsuitable for, medical treatment. The hysterectomy rate in 1980 in this country was under 20% (van Keep *et al* 1983), but rates are higher in some other countries. In the early 1970s in the USA, a young woman had a 50% chance of undergoing hysterectomy during her life-time (Bunker 1976), and a similar calculation for a group of women with medical insurance in Australia (Selwood & Wood 1978) produced a figure of 40%. Such high rates of surgical intervention have been widely criticized. There is no reason to believe that the occurrence of menorrhagia varies from country to country. No more than 22% of premenopausal women over the age of 34 report any symptoms (Gath *et al.* 1987) so a hysterectomy rate of 50% is incompatible with the treatment of a condition that has a maximum prevalence of 22%. The reasons for this discrepancy are likely to relate more to the attitude of women and of doctors towards menstruation than to variations in occurrence of pathology

There is no doubt that hysterectomy is a highly effective way to treat menorrhagia. For a major surgical procedure, mortality is exceedingly low, only 6/10 000 procedures (Wingo *et al* 1985). Why then is there a need for change and improvement in management? Operative morbidity is not insignificant (Dicker *et al.* 1982) and is greatly increased when complications occur. Postoperative stay is about 1 week, but about 6 weeks convalescence is usual. The cost of this treatment is considerable

With regard to long-term morbidity, hysterectomy for menorrhagia on average hastens the onset of menopausal symptoms, due to oestrogen deficiency, by about 4 years (Siddle *et al* 1987). These symptoms may occur earlier the younger the woman is at the time of operation. Also, there seems to be about a threefold increase in the incidence of coronary heart disease from the time of operation till the age of 50 (Centerwall 1981). Other long-term complications such as micturition difficulties, prolapse or pelvic pain have been associated with hysterectomy, but evidence that a large number of women are affected in this way is hard to find. Similar comments apply to psychiatric morbidity following hysterectomy. There is no doubt that hysterectomy can be an emotionally and physically traumatic procedure, but current evidence suggests that psychiatric symptoms are certainly not exacerbated and are possibly reduced after hysterectomy for menstrual dysfunction (Gath & Cooper 1981). In support of the procedure, 90% of women are satisfied with the operation (van Keep *et al.* 1983). But can hysterectomy be justified, even in the face of patient satisfaction, if an alternative and minor procedure is available?

Is there a need for more conservative therapy? Selective endometrial destruction offers a hope of less radical surgery. The case for this technique resides in the fact that menorrhagia is rarely a life-threatening condition and 50% of hysterectomy specimens removed for this indication are entirely normal on pathological examination (Grant & Hussain 1984). Menstrual blood loss is entirely endometrial in origin and there is increasing support for the view that many of the mechanisms involved in menstrual dysfunction reside in the endometrium. Therefore, if it is only the endometrium which is at fault its selective destruction or removal should be as successful as hysterectomy. Evidence to date suggests that this is correct.

Techniques at present available for endometrial destruction involve either laser or electrical energy and are performed under hysteroscopic control. Hysteroscopic neodymium-YAG laser ablation of the endometrium has been used effectively for 10 years (Goldrath 1985). In expert hands, results are impressive with success rates of 93%, evidenced by subsequent amenorrhoea in 50% and only light menstrual blood loss in the remainder. There are, however, a few problems The procedure may be difficult and time consuming. The laser is expensive and few surgeons have matched the above results (Davies 1989). Instrument companies have been slow to develop a continuous-flow hysteroscope which gives a clear and reliable view throughout the treatment. High-presure and high-flow irrigation will compensate for an inadequate instrument, but carries a significant risk of fluid overload. Postoperatively the uterine cavity may become completely obliterated. Theoretically, residual endometrium may become neoplastic which may be recognized late because of the absence of postmenopausal bleeding, although to date no cases have been reported and logically, destruction of the endometrium should diminish the risk of endometrial carcinoma. To minimise the risk, laser ablation is only advocated for women with excessive and regular menstruation without evidence of endometrial hyperplasia. Immediate postoperative problems are rare and recovery is rapid. Moderate blood loss occurs for about a week and watery discharge for a further 2 weeks Laser ablation may be a day-care procedure and the women can resume normal activities within a few days.

The urological resectoscope has been used successfully to remove the endometrium (DeCherney *et al.* 1987). High-frequency diathermy is used to charge the resectoscope loop, and a safe and precise tissue cut can be achieved with minimal surrounding coagulation The endometrium can be resected quickly and satisfactory histological sections can be obtained from the resected chips. Resectoscopes with continuous-flow irrigation systems already exist and a clear view of the uterine cavity can be achieved with low intrauterine pressures. Meticulous attention to irrigation fluid pressure and inflow–outflow balance is essential to avoid the potentially serious complication of fluid overload. This is particularly important when using the non-electrolytic solution glycine. Absorption of this solution may cause the 'TUR syndrome', the effects of which are not entirely understood and are not simply related to volume. Improved hysteroscope design with more attention to the characteristics and efficiency of intrauterine flow will make the procedure easier and safer.

There are few published reports of follow-up after endometrial resection. DeCherney *et al.* (1987) and Magos *et al.* (1989) describe the procedure and report short-term follow-up. These indicate that in the short term, endometrial resection is as effective as laser ablation. Many larger series do exist, but as yet are unpublished.

The resectoscope can also be used for rollerball electrocoagulation. The endometrium is coagulated by a diathermy current which is applied by running a ball over the endometrial surface. The procedure can be performed very quickly and easily and, theoretically, should have the same effect as laser ablation. Short-term results are encouraging (Vancaille 1989), but longer follow-up is necessary for adequate assessment.

Hysteroscopic surgery, although in its infancy, has enormous potential. Not only does it promise efficient treatment of menorrhagia, but there would be considerable financial savings for health care services. Each year in the UK about 70 000 (DHSS and OPCS 1985) hysterectomies are performed and in about two-thirds of these menorrhagia is the indication. If two-thirds of this latter group were treated hysteroscopically £25 000 000 would be saved from reduced bed occupancy alone [6 days/patient×£135/bed-day (cost in 1988 of one bed-day in Royal Northern Hospital, London)×30 500].

In the near future it is probable that a large number of hysterectomies will be replaced by these endoscopic procedures. However, there are aspects of the technique that need refinement, especially the problem of fluid overload. For financial reasons the resectoscope seems the better instrument, but any method which results in complete removal or destruction of the endometrium is likely to be effective. Long-term problems are unlikely to be significant but will not be known for some time. The apparent benefits of the technique are likely to lead to the rapid adoption of the hysteroscopic management of menorrhagia. There is an urgent need to organize long-term follow-up studies, in case the short-term benefits for the majority are followed by serious problems for a few.

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Advances in the treatment of the premenstrual syndrome

In many respects, the premenstrual syndrome (PMS) is an ill-understood a subject now as when it was first formally described by Frank (1931). Our confusion is no better demonstrated than in the pages of reputable journals, where disagreement concerning definition, diagnostic criteria, pathophysiology, and therapy is the norm rather than the exception. If the scientists cannot come to a consensus, it is not surprising that the busy clinician, often armed with more doubt than interest, finds the management of these patients difficult. Yet treat we must, so the question remains: how best can we help women who complain of cyclical premenstrual distress?

Successful treatment depends on correct diagnosis, an understanding of the underlying pathology, and reliable means of assessing therapy. In the field of PMS research, advances have been made recently with respect to all three aspects.

Firstly, it is now generally agreed that a diagnosis of PMS can only be made with any degree of confidence by some form of objective symptom assessment. History, particularly in the women who are not severely affected, can often be misleading (Ablanalp *et al.* 1979). Daily prospective symptom recordings analysed according to statistically meaningful techniques have become the 'gold standard' and, ideally, should always be used before a diagnostic judgement is made. Such assessment need not be complicated to be relevant (Magos & Studd 1988).

Secondly, there is a growing acceptance that PMS is a function of cyclical ovarian activity. Menstruation *per se* is not fundamental as shown by symptom monitoring before and after hysterectomy (Backstrom *et al.* 1981). The importance of ovulation was realized by Studd (1979) but it is only recently that support for this hypothesis has been forthcoming. Nine years later for instance, Hammarback & Backstrom (1988) have suggested that a 'factor from the corpus luteum must be involved in aetiology'. The nature of this factor, if it exists, is as yet unknown, but it is perhaps pertinent that no reliable and reproducible biochemical marker has been found to differentiate sufferers from asymptomatic controls. The parallel view that PMS is the end result of the influence of the many physiological changes that normally accompany cyclical ovarian activity in susceptible women may be equally true (Magos 1989).

Thirdly, increasing awareness of the extent of the placebo response has meant that earlier uncontrolled treatment studies are virtually meaningless. A figure of 50% for the placebo response is often quoted, but this seems an underestimate at least at the start of therapy as a placebo response of up to 89% has been reported with oral medication (Mattsson & von Schoultz 1974), the rate rising to 94% with surgically inserted hormone implants (Magos *et al.* 1986). A controlled comparison with placebo has thus become an essential prerequisite to proof of efficacy for any therapy.

That said, placebo-controlled studies can be misleading and must be assessed critically. On the one hand, if the response to placebo is unusually weak, a relatively ineffective treatment may seem significantly superior (Type I statistical error). Conversely, if the duration of comparison with the active agent is too short and insufficient time is allowed for the placebo response to wane, a false conclusion of inefficacy may be made (Type II statistical error). There is as yet only circumstantial evidence concerning the duration of the placebo response in PMS; for instance, in our study the response to placebo implants was negligible after ten months of treatment (Magos *et al.* 1986). Treatment studies can be further perverted by the use of too many end points, the investigators concentrating only on those which show a positive result.

What are the implications then for treatment? Clearly, studies must fulfil certain criteria to be meaningful and I consider the following important: (1) diagnosis of PMS based on prospective symptom assessment; (2) treatment subject to double-blind placebo-controlled study; (3) symptoms assessed daily during the study; (4) follow-up period at least three months; (5) placebo response at least 50%; (6) significant benefit of active treatment over placebo for at least 50% of variables studied. It is only by applying such rules to study design and assessment that we are likely to come to correct conclusions. With our current understanding, therapies aimed at specific (and hypothetical) abnormalities are unlikely to succeed any more than placebo. Instead, treatments should be aimed at preventing whatever event(s) in the luteal phase of the cycle precipitate symptoms. Until the precise pathophysiology of premenstrual distress is identified, and as noted earlier it is not unlikely that multiple factors are involved, this means suppression of *all* luteal-phase changes by inhibition of cyclical ovarian activity. This is indeed the only therapeutic strategy that has consistently been shown by independent investigators using a variety agents to be effective for the management of PMS (Table 1).

Interestingly, the combined oral contraceptive pill has not yet been tested under controlled conditions for PMS, although it is relevant that it has been shown to be of benefit in the management of other cyclical disorders which are exacerbated premenstrually such as catamenial epilepsy (Rossi & Goplerud 1974), diabetes (Sandstrom 1969), acute intermittent porphyria (Pelroth *et al.* 1965) and periodic hypersomnia (Sachs *et al.* 1982). Instead, attention has been focused on danazol, oestradiol implants, and most recently LHRH agonists

As with the combined contraceptive pill, danazol was found to improve the premenstrual exacerbations of systemic lupus erythematosus (Morley *et al.* 1982). In PMS, beneficial effects have been reported from controlled studies using continuous danazol doses of 100–400 mg daily, but treatment was associated with high withdrawal rates (Gilmore *et al.* 1985; Watts *et al.* 1985, 1987). It may be that side-effects can be prevented by restricting medication to the premenstrual phase of the cycle as suggested by the small study of Sarno *et al.* (1987). Symptomatic side-effects apart, the adverse metabolic actions and, not least, cost are other factors to consider with long-term treatment.

Anovulatory doses of subcutaneous implants of oestradiol combined with a cyclical oral progestogen to prevent endometrial hyperplasia were shown to be statistically superior to placebo for all symptoms monitored despite an initial response to placebo implants of 94% (Magos *et al.* 1986). This combination is usually well tolerated, but a degree of commitment is required from patients because of the prolonged action of implants. The recent introduction of 'Estraderm' skin patches is an attractive alternative to implants, and preliminary results are equally encouraging (N. Watson & J. W. W. Studd, personal communication).

Finally, LHRH agonists can be used to inhibit ovulation and thus cyclical mood changes, as shown by Hammarback & Backstrom (1988). However, adverse effects can mean that long-term treatment may be effective in only 50% of women (Bancroft *et al.* 1987). There must also be concern about the metabolic sequelae of prolonged hypo-oestrogenaemia when high doses are administered, or conversely endometrial hyperplasia with low-dose treatment, when plasma oestrogen concentrations are not suppressed but ovulation is.

As can be seen from Table 1 there are occasional exceptions to successful treatment with agents other than those which induce anovulation. Almost all are isolated reports which have not been replicated by other workers. The most convincing data derive from a recent, carefully designed study by Mira *et al.* (1986) which showed that several but not all of the typical symptoms of PMS were significantly improved by the prostaglandin synthetase inhibitor mefenamic acid. It may be that the beneficial effect of prostaglandin synthetase inhibitors is related to modification of the ovulatory process as shown

Table 1. Results of placebo-controlled studies of treatments for the premenstrual syndrome

Treatment	Results of placebo-controlled studies		
	Effective	Equivocal	Not effective
Progesterone	—	Dennerstein *et al* (1985)	Smith (1975) Sampson (1979) Van der Meer *et al* (1983) Andersch & Hahn (1985) Maddocks *et al.* (1986)
Progestogens	—	Williams *et al* (1983)	Jordheim (1972) Haspels (1981) Ylostalo *et al* (1982) Sampson *et al* (1986) Dennerstein *et al* (1986)
Pyridoxine	Abraham & Hargrove (1980) Mattes & Martin (1983) Barr (1984)	Williams *et al* (1985)	Stokes & Mendels (1972) Hagen *et al* (1985)
Diuretics	Coppen *et al* (1972) Wersch & Kane (1976) Hoffman (1979)	O'Brien *et al* (1979) Carstairs & Talbot (1981)	Reeves *et al* (1971) Jordheim (1972) Mattsson & von Schoultz (1974) Smith (1975)
Bromocriptine	Philipp (1977) Andersch *et al* (1978) Graham *et al* (1978) Ylostalo *et al* (1981)	Benedek-Jaszmann & Hearn-Sturtevant (1976) Andersen *et al.* (1977) Elsner *et al* (1980)	Harrisson & Letchworth (1976) Ghose & Coppen (1977) Kullander & Svanberg (1979)
Psychoactive drugs	Rickels *et al* (1989)	Smith *et al* (1987)	Mattsson & von Schoultz (1974) Singer *et al* (1977) Steiner *et al.* (1980)
Prostaglandin mediators	Mira *et al* (1986)	Wood & Jakubowicz (1980) Poulakka *et al* (1985) Ylikorkala *et al* (1986)	—
Miscellaneous	Prior *et al* (1987) Chuong *et al* (1988)	Robinson *et al* (1977) Atton-Chamla *et al* (1980)	—
Danazol	Gillmore *et al.* (1985) Watts *et al.* (1985 & 1987) Sarno *et al* (1987)	—	—
Oestrogens	Magos *et al.* (1986) Watson & Studd (1989)	—	—
LHRH agonists	Muse *et al.* (1984) Hammarback & Backstrom (1988)	Bancroft *et al.* (1987)	—

A complete list of references quoted in this Table is available from the Journal office on request

by Priddy *et al.* (1989). With the putative role of endogenous opiate peptides, the generally favourable results of treatment with the opiate antagonist naltrexone (Chuong *et al.* 1988) are of interest, providing perhaps a clue to the central side of this psycho-endocrine disorder. Recent studies involving the benzodiazepine derivative alprazolam (Smith *et al* 1987) and buspirone (Rickels *et al.* 1989), a non-sedating, non-benzodiazepine anxiolytic, have also reported favourable results, but the studies were associated with either minimal improvement after placebo (which puts in question the criteria for patient selection) or insufficient data for critical analysis. Other less convincing suggestions include the use of an alkaloid/ergotamine/barbiturate mixture of 'bellergal' (Robinson *et al* 1977), desensitization with gammaglobulin/histamine complex (Atton-Chamla *et al.* 1980), and conditioning exercise (Prior *et al.* 1987). Methodological and other considerations suggest the need for confirmatory data before any of these treatments can be widely recommended. In contrast, there is a mass of data attesting to the inefficacy of the traditional therapies such as progesterone, progestogens, pyridoxine, diuretics, bromocriptine and lithium (Table 1).

In conclusion, a rational approach to the management of PMS is becoming clear. Make the correct diagnosis using prospective symptom assessment. Always counsel, reassure and explain, avoid stress and resolve concurrent problems, measures which may be sufficient in women with mild symptoms. Women with moderate symptoms need more direct help, and mefenamic acid (or perhaps the combined contraceptive pill) should be tried. Anovulatory therapy seems the only answer in those with severe symptoms. The ultimate, if drastic solution, as for so many gynaecological problems, must be hysterectomy with bilateral salpingo-oophorectomy combined with oestrogen replacement, although controlled proof is lacking.

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Addendum

A complete list of references to Table 1 is available from the Journal office on request

British Journal of Obstetrics and Gynaecology
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The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials

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Summary. Continuing differences of opinion among obstetricians and neonatologists about the place of corticosteroid administration before preterm delivery have prompted us to carry out a systematic review of the relevant controlled trials, using methods designed to minimize systematic and random error. Data from 12 controlled trials, involving over 3000 participants, show that corticosteroids reduce the occurrence of respiratory distress syndrome overall and in all the subgroups of trial participants that we examined. This reduction in respiratory morbidity was associated with reductions in the risk of intraventricular haemorrhage, necrotizing enterocolitis and neonatal death. There is no strong evidence suggesting adverse effects of corticosteroids. The risks of fetal and neonatal infection may be raised if they are administered after prolonged rupture of the membranes, but this possibility is not substantiated by the results of the available trials. The available data on long-term follow-up suggest that the short-term beneficial effects of corticosteroids may be reflected in reduced neurological morbidity in the longer term.

In the course of investigating the initiation of labour in sheep, Liggins (1969) observed that lambs born preterm after exposure to corticosteroids *in utero* survived longer than control lambs. A subsequent randomized, placebo-controlled trial of betamethasone administration in women who were expected to be give birth preterm found a statistically significant reduction in the frequency of respiratory distress in babies born before 32 weeks gestation and a fivefold reduction in neonatal mortality among preterm babies born after corticosteroid compared with placebo administration (Liggins & Howie 1972).

Since these classic studies, several further investigations have suggested that antenatal administration of corticosteroids reduces neonatal morbidity. However, 18 years after the trial described by Liggins & Howie (1972) there continues to be variation in obstetricians' use of antenatal corticosteroids in women who are expected to give birth preterm. A survey of practice among fellows and members of the Royal College of Obstetricians and Gynaecologists resident in the UK showed that 42% used this

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treatment 'frequently', 40% 'sometimes', and 18% 'never' (Lewis *et al.* 1980). In a similar study of obstetricians in northern Belgium and the Netherlands, Keirse (1984) also found a wide variation in practice, with only 32·5% of respondents using the treatment 'routinely'.

These variations in practice among obstetricians reflect differing interpretations of the evidence of efficacy and safety of antenatal corticosteroid therapy. Differences of opinion also exist among neonatologists. Roberton (1982) for example suggested that corticosteroids only benefit white, male infants, and that, even for them, the benefit is mainly among those born between 30 and 32 weeks gestation. Avery (1984) by contrast has condemned the obstetric community's failure to accept antenatal corticosteroid administration as 'an essential intervention to prevent respiratory distress syndrome'.

These differences of opinion may, in part, result from overemphasis on the results of a single trial, or a secondary analysis within a particular trial. Because the sample sizes of individual trials are relatively small, estimates of the effects of corticosteroids are likely to vary widely as a result of the play of chance (random error). Investigators may sometimes have concluded that differences between corticosteroids and placebo did not exist because the differences were not statistically significant in these trials and subgroup analyses.

In an attempt to clarify the extent to which these phenomena have led to conflicting opinions, which obviously exist among clinicians, we have incorporated data derived from as high a proportion as possible of all relevant placebo-controlled, randomized trials in a single analysis. In this way, we have attempted to minimize not only systematic error (bias), but also random error (the play of chance).

Materials and methods

Identification and selection of relevant studies

We attempted to locate all published reports of controlled trials of corticosteroid use in threatened or planned preterm delivery using the Oxford Database of Perinatal Trials (Chalmers 1988). (Details of the database and the completeness of its coverage of perinatal trials are available elsewhere: Dickersin *et al.* 1985; Chalmers *et al.* 1986, 1989.) In an attempt to locate unpublished trials, letters were sent to 42 000 obstetricians and paediatricians in 18 countries (Hetherington *et al.* 1989).

Using these two approaches, we identified a total of 23 potentially relevant trials. On closer analysis, four of these proved not to be randomized controlled trials (Baillie *et al.* 1976; Dluholucky *et al.* 1976; Kleinschmidt *et al.* 1977; Szabo *et al.* 1977), and one had amalgamated randomized with non-randomized cases (Simpson & Harbert 1985); so these five trials were excluded. Three trials (Farrell *et al.* 1983; Gunston & Davey 1978; Whitt *et al.* 1976) assessed the effects of antenatal corticosteroid administration only in terms of the results of laboratory tests (e.g. lecithin: sphyngomyelin ratios); these were also excluded from our analysis, since clinical data were not available.

In three of the remaining 15 trials, allocation had not been simply to either corticosteroid administration or no administration of corticosteroids, but to a larger 'package of care' of which corticosteroid administration was but one component (Garite *et al.* 1981; Iams *et al.* 1985; Nelson *et al.* 1985); these trials were excluded from the main analysis. All three of the trials in this last category involved women with prelabour rupture of the membranes (PROM) preterm who were not in labour at the time of admission to the study. Data from these trials have therefore been included in a secondary analysis, restricted to women with PROM.

Data presented in multiple reports of the same trial have been amalgamated (*the New Zealand trial:* Liggins & Howie 1972, 1973, 1974; Howie & Liggins 1973, 1977, 1980, 1982; Liggins 1976; *the (US) Collaborative Group on Antenatal Steroid Therapy* 1981, 1984; Bauer *et al.* 1984; Burkett *et al.* 1986; Schneider *et al.* 1988; and *the Amsterdam trial:* Schutte *et al.* 1979, 1980, 1983). Because failure to report the outcome of all cases randomized and selective reporting of data on relevant outcomes may lead to biased estimates of treatment effects, we contacted investigators in an effort to obtain missing data. We are indebted to the investigators who helped us in this way (see Acknowledgments).

A total of 12 trials, involving over 3000 women, was thus available for the main analysis. Table 1 lists the entry and exclusion criteria, treatment and diagnostic regimens and completeness of reporting for these 12 trials. Four of the 12 trials (Block *et al.* 1977; Collaborative Group on Antenatal Steroid Therapy 1981; Schmidt *et al.* 1984; Morales *et al.* 1986) pro-

Table 1. Characteristics of the randomized controlled trials of corticosteroid administration

Authors and date	Entry criteria	Exclusion criteria	Treatment regimen	No. reported. no. randomized
Liggins & Howie (1972); Howie & Liggins (1977)	Threatened or planned preterm delivery 25–37 weeks	Imminent delivery; 'clinical decision not to randomize'	Betamethasone 12 mg i.m. in 2 doses 24 h apart	1070:1135 (65 with lethal malformations)
Block *et al.* (1977)	Women judged to be in preterm labour	Not stated	Betamethasone 12 mg i.m in 2 doses 24 h apart	155:175
Morrison *et al.* (1978)	Threatened or planned preterm delivery if <34 weeks or immature L/S ratio	Imminent delivery; mature L/S ratio; medical contraindication to corticosteroids	Hydrocortisone 500 mg i.v. in 4 daily doses at 12-h intervals	126–196
Papageorgiou *et al.* (1979)	Preterm labour or PROM at 26–33 weeks	Diabetes; hypertension; pre-eclampsia; rhesus disease; retarded fetal growth	Betamethasone 12 mg i m in 2 doses 12 h apart	131:146
Schutte *et al.* (1979)	Preterm labour 27–31 weeks 'if it seemed possible to postpone labour for 12 h'	Diabetes; severe hypertension; retarded fetal growth; hyperthyroidism; cardiac disease; fetal distress; infection	Betamethasone phosphate 8 mg + betamethasone acetate 6 mg in 2 doses i.m. 24 h apart	122 122
Taeusch *et al* (1979)	Preterm labour or PROM either <34 weeks with immature L/S ratio or with previous infant with RDS	Cervix 5 cm dilated, severe bleeding; chorioamnionitis; severe pre-eclampsia; pre-existing glucocorticoid therapy	Dexamethasone 4 mg i.m. in 6 doses at 8-h intervals	127:127
Doran *et al.* (1980)	Preterm labour or PROM, or planned preterm delivery at 25–33 weeks	Pre-eclampsia; medical contra-indication to corticosteroid therapy	Betamethasone 6 mg i.m. in 4 doses at 12-h intervals	144.144
Teramo *et al* (1980)	Preterm labour at 29–35 weeks, cervix <4 cm dilated, no precipitous progression after 12 h observation	Diabetes; pre-eclampsia	Betamethasone 12 mg i.m. in 2 doses 24 h apart	80:80

PROM, Prelabour rupture of the membranes

Table 1 (continued). Characteristics of the randomized controlled trials of corticosteroid administration

Authors and date	Entry criteria	Exclusion criteria	Treatment regimen	No. reported: no. randomized
Collaborative Group on Antenatal Steroid Therapy (1981)	Women with 'high risk for premature delivery' at 27–33 weeks; with 'high risk' >34 weeks and L/S ratio ≤2·0	Cervix 5 cm dilated; delivery anticipated in <24 h or >7 days; intrauterine infection; previous corticosteroid therapy in pregnancy; medical contraindication to corticosteroid therapy; infant unavailable for follow-up	Dexamethasone 5 mg i.m. in 4 doses	739:757
Schmidt *et al.* (1984)	Preterm labour or PROM at 25–33 weeks or with estimated fetal weight 750 g	Cervix 5 cm dilated; medical contraindication to corticosteroid therapy; 'deemed unsafe to delay delivery for 24 h'	Betamethasone 12 mg in 2 doses 24 h apart; methylprednisolone 125 mg in 2 doses 24 h apart; hydrocortisone 250 mg in 2 doses 24 h apart	97:149
Morales *et al.* (1986)	Women with PROM	Labour on admission, foul-smelling amniotic fluid; retarded fetal growth; phosphatidyl glycerol present	Dexamethasone 6 mg i.m. in 4 doses at 12-h intervals	245:250
Gamsu *et al.* (1989)	Spontaneous labour or elective induction at <34 weeks	Diabetes; chorioamnionitis, contraindication to corticosteroid therapy; when delay of delivery for 24 h was not in the maternal or fetal interest	Betamethasone 4 mg i.m. in 6 doses at 8-h intervals over 48 h	251:251 (268 babies)

PROM, Prelabour rupture of the membranes.

Table 2. Characteristics of the randomized controlled trials of corticosteroid administration combined with other treatment options for women with prelabour rupture of the membranes (PROM)

Study	Entry and exclusion criteria No. treated and controls	Corticosteroid group	Control group
Garite *et al.* (1981)	Entry: 28–34 weeks Excluded: chorioamnionitis; advanced labour; fetal distress, mature L/S or positive Gram stain on amniocentesis No treated: 80 No. control: 80	Betamethasone 12 mg in 2 doses 24 h apart + tocolytic treatment (ethanol or magnesium sulphate) for 48 h, delivery effected after 48 h by discontinuing tocolytic treatment, inducing labour, or caesarean section	'Expectant management'; delivery was performed only when either labour, chorioamnionitis or fetal distress occurred
Iams *et al.* (1985)	Entry: 28–34 weeks, singleton pregnancy, not in labour and not infected Excluded: mature amniotic fluid L/S ratio or phosphatidyl glycerol determination No treated 38 No. control. 35	Hydrocortisone 500 mg i.v. in 4 doses at 8-h interval; tocolytics if necessary to delay delivery until 12 h after corticosteroid treatment; delivery effected at 48–72 h by discontinuing tocolysis, induction of labour or caesarean section	No corticosteroids; no tocolysis, delivery only when labour, amnionitis or fetal distress developed
Nelson *et al.* (1985)	Entry: 28–34 weeks; not in labour and not infected Excluded: cervix >3 cm; fetal distress; sensitivity to tocolytics; membranes ruptured for >24 h No treated: 22 No. control: 22* + 24	Betamethasone 6 or 12 mg in 2 doses 12 hours apart + ritodrine or terbutaline for 24 h; delivery effected after full 24 h corticosteroid treatment	Non-steroid group treated identically (including delivery)* Second control group without steroid and tocolytic treatment followed expectantly

* Only this control group was used for the data shown in Tables 9 and 10

vided separate data on women with PROM. These data have been incorporated in the secondary analysis of this subgroup of women, along with data from the three additional trials referred to above (Table 2).

Methodological quality of the published studies

In addition to the requests for missing data, authors were asked, where necessary, to provide information on their study methods. This enabled us to assess the methodological quality of each study in terms of control of bias at entry, control of selection bias after entry, and control of observer bias in assessing outcomes. The criteria we used to assess the likely influence of these three sources of bias have been described elsewhere (Prendiville *et al.* 1988; Chalmers *et al.* 1989). The trials included in this overview are generally of high methodological quality; but in each array of trial results presented below, studies have been ranked according to our assessment of the likelihood that the comparisons may have been biased. Trials of equivalent quality were ranked by date of publication.

Statistical methods

The results of each trial have been presented using the odds ratio together with its 95% confidence interval (CI). The odds ratio is the ratio of the odds of a negative outcome (for example, respiratory distress) *versus* a positive outcome (no respiratory distress) among those allocated to corticosteroids, to the odds of the negative outcome *versus* the positive outcome among the controls. Because random variation may lead the odds ratio in individual trials to be overestimated or underestimated, we used methods described by Peto and his colleagues (Peto *et al.* 1976; Collins *et al.* 1985; Yusuf *et al.* 1985) to analyse data within the framework of an overview (meta-analysis) of information derived from each of the relevant trials identified (Chalmers *et al.* 1989). The effect of corticosteroids in each trial is measured by $O-E$, where O is the observed number of individuals suffering the outcome in question among those allocated corticosteroids, and E is the number that would have been expected on the basis of the experience of the corticosteroid and placebo groups combined. The sum of the differences derived from each individual trial [$\Sigma\ (O-E)$], combined with the sum of the variances of these differences [$\Sigma\ \mathrm{Var}\ (O-E)$], have been used to provide an estimate of a 'typical odds ratio':

$$\mathrm{Exp}\ (\Sigma\ (O-E)/[\Sigma\ \mathrm{Var}\ (O-E)]).$$

This statistic is an expression of any tendency that may exist for those receiving steroids to do better or worse than those who received placebo. Its 95% CI is calculated as follows:

$$\mathrm{Exp}\ [\Sigma\ (O-E)/\Sigma\ \mathrm{Var}\ (O-E)] + 1{\cdot}96/\Sigma\ \mathrm{Var}\ (O-E)$$

Results

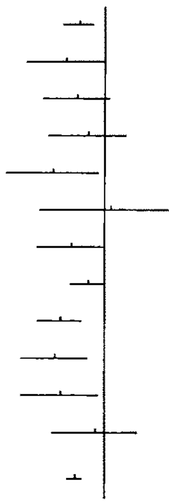
Neonatal respiratory distress

The occurrence of neonatal respiratory distress is the principal outcome reported in the 12 eligible trials identified. The data presented in Table 3 show that antenatal corticosteroid administration is associated with an overall reduction of about 50% in the odds of this form of neonatal morbidity (typical odds ratio 0·49, 95% CI 0·41–0·60).

In a secondary analysis stratified by time interval between trial entry and delivery, the point estimate of a 70% reduction in the odds of developing respiratory distress (typical odds ratio 0·31, 95% CI 0·23–0·42) among babies born between 24 h and 7 days after corticosteroid administration suggests that the protective effect is more marked in these circumstances, and this is biologically plausible. Nevertheless, babies born outside this time interval also benefit, albeit to a lesser extent (typical odds ratio 0·69, 95% CI 0·50–0·94) (Fig. 1).

There is no evidence to support the view that the effect on the incidence of respiratory distress is confined to babies born within a particular gestational age range. Most of the babies randomized in these trials were born between 30 and 34 weeks gestation; the overall results thus tend to reflect the experiences of these babies in particular. Nevertheless, analyses based on data derived from the seven trials from which data are available show that corticosteroid administration is followed by an unambiguous and important reduction in the risk of respiratory morbidity among babies born at less than 31 weeks gestation (typical odds ratio 0·38, 95% CI 0·24–0·60) (Table 4). Respiratory distress is such a rare condition among babies born after 34 weeks gestation that the available data yielded only 29 affected babies from eight trials. The

Table 3. Effect of corticosteroids before preterm delivery on respiratory distress, overall

	Treated		Control		Odds ratios and 95% CI	
					Numerical	Graphical
Study	*n*	(%)	*n*	(%)		0·1 0·5 1 2 10
Liggins & Howie (1972)	49/532	(9·21)	84/538	(15·61)	0·56 (0·39–0·80)	
Block *et al* (1977)	5/69	(7·25)	12/61	(19·67)	0·34 (0·12–0·94)	
Schutte *et al.* (1979)	11/64	(17·19)	17/58	(29·31)	0·51 (0·22–1·18)	
Taeusch *et al* (1979)	7/56	(12·50)	14/71	(19·72)	0·60 (0·23–1·52)	
Doran *et al* (1980)	4/81	(4·94)	10/63	(15·87)	0·29 (0·10–0·88)	
Teramo *et al* (1980)	3/38	(7·89)	3/42	(7·14)	1·11 (0·21–5·83)	
Gamsu *et al.* (1989)	7/131	(5·34)	16/137	(11·68)	0·45 (0·19–1·05)	
Collaborative Group (1981)	42/371	(11·32)	59/372	(15·86)	0·68 (0·45–1·03)	
Morales *et al* (1986)	30/121	(24·79)	63/124	(50·81)	0·33 (0·20–0·56)	
Papageorgiou *et al* (1979)	7/71	(9·86)	23/75	(30·67)	0·28 (0·13–0·63)	
Morrison *et al* (1978)	6/67	(8·96)	14/59	(23·73)	0·33 (0·13–0·87)	
Schmidt *et al.* (1984)	9/34	(26·47)	10/31	(32·26)	0·76 (0·26–2·20)	
Typical odds ratio					0·49 (0·41–0·60)	

typical odds ratio of 0·62 and its 95% CI (0·29–1·30) is, however, consistent with those derived from other subgroups, although (because it includes 1·0) it is also compatible with chance variation.

There is no evidence from the few available data that infant gender influences the protective effect of corticosteroids on the risk of neonatal respiratory distress described above. The typical odds ratio for males is 0·43 (95% CI 0·29–0·64); for females it is 0·36 (95% CI 0·23–0·57) (Fig. 1).

The separate analysis of corticosteroid administration after PROM (see below) indicates a reduction in neonatal respiratory morbidity of a similar order to that described for other subgroups.

In summary, we have not been able to identify any subgroup of babies for which it can be con-

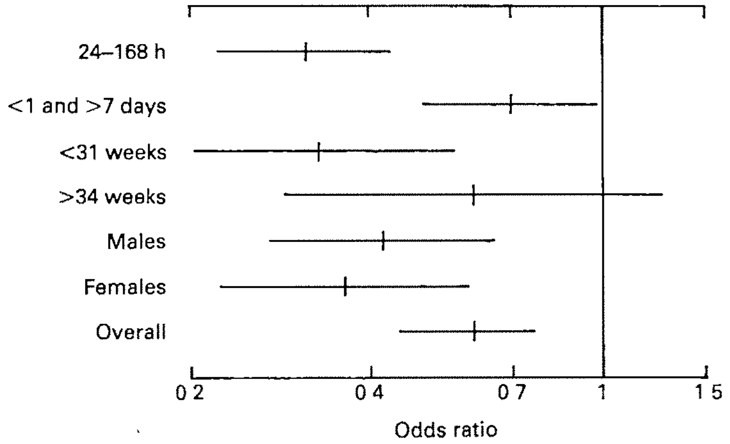
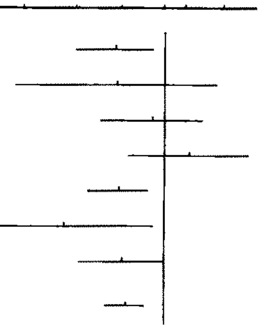


Fig. 1. Effects of corticosteroid administration before preterm delivery on the occurrence of neonatal respiratory distress, by interval between corticosteroid administration and delivery, gestational age at delivery, and infant gender (typical odds ratio and 95% confidence interval)

Table 4. Effect of corticosteroids before preterm delivery on respiratory distress in babies <31 weeks gestation

Study	Treated		Control		Odds ratios and 95% CI	
					Numerical	Graphical
	n	(%)	*n*	(%)		0·01 0·1 0·5 1 2 10
Liggins & Howie (1972)	10/36	(27·78)	15/26	(57·69)	0·29 (0·11–0·82)	
Taeusch *et al* (1979)	1/3	(33·33)	4/6	(66·67)	0·33 (0·02–4·18)	
Gamsu *et al* (1989)	4/29	(13·79)	7/39	(17·95)	0·74 (0·20–2·70)	
Collaborative Group (1981)	6/10	(60·00)	7/16	(43·75)	1·87 (0·40–8·80)	
Morales *et al* (1986)	17/53	(32·08)	32/52	(61·54)	0·31 (0·14–0·66)	
Papageorgiou *et al* (1979)	2/5	(40·00)	11/12	(91·67)	0·07 (0·01–0·73)	
Morrison *et al* (1978)	6/36	(16·67)	11/28	(39·29)	0·32 (0·11–0·97)	
Typical odds ratio					0·38 (0·24–0·60)	

cluded that corticosteroid administration before preterm delivery is *not* associated with a reduction in the risk of neonatal respiratory morbidity (Fig. 1).

Other forms of neonatal morbidity

In addition to promoting functional maturation of the fetal lungs, corticosteroids may have similar 'primary' effects on other organs. Furthermore, because corticosteroids reduce the risk of respiratory morbidity, they might be expected to have 'secondary' effects by reducing those complications of respiratory morbidity and its treatment which involve other organ systems. The data available for examining this possibility are limited, but they suggest that the odds of both periventricular haemorrhage and necrotizing enterocolitis are reduced by anything between 10 and 80% after corticosteroid administration (Fig. 2). The reduction in serious neonatal morbidity is likely to explain the statistically significantly shorter mean durations of hospital stay among cortiscosteroid-treated infants in the two trials for which these data were reported (Collaborative Group on Antenatal Steroid Therapy 1981; Morales *et al.* 1986).

Early neonatal mortality and morbidity in later infancy

These significant reductions in serious forms of neonatal morbidity are reflected in a substantial reduction in the risk of early neonatal mortality (typical odds ratio 0·59, 95% CI 0·47–0·75) (Table 5).

It is important to assess whether this reduction in the risk of death was achieved at the cost of an increased prevalence of morbidity among survivors. Because of the reduced neonatal mortality rate in corticosteroid-treated babies, survivors in the corticosteroid arms of these trials had a lower mean gestational age at delivery than survivors in the control groups. In the light of this difference, one might expect survivors in the corticosteroid groups to be more likely to have impaired function than survivors in the control groups

Three follow-up studies have been published (Butterfill & Harvey 1979; MacArthur *et al.* 1981, 1982, 1989; Collaborative Group on Antenatal Steroid Therapy, 1984). Unfortunately, the study reported by Butterfill & Harvey (1979) amalgamated non-randomized with randomized cohorts, and it is not now possible to disaggregate the data to allow unbiased comparisons to be made between the steroid-treated and the control groups (Harvey, personal communication). Data from the two studies that followed up surviving members of randomized cohorts are reassuring. If anything, they suggest that neurological abnormalities are less frequent among babies whose mothers received corticosteroids than among controls (typical odds ratio 0·61, 95% CI 0·34–1·08) (Table 6).

Possible fetal, neonatal and maternal risks

The randomized trials analysed here do not provide any evidence that fetal exposure to corticosteroids is accompanied by any increased risk of fetal death: stillbirth occurred with almost identical frequency in the two groups (odds ratio 1·03, 95% CI 0·68–1·54). In the subgroup of participants who had pre-eclampsia in the Auckland trial (Howie & Liggins 1977), there were 12 fetal

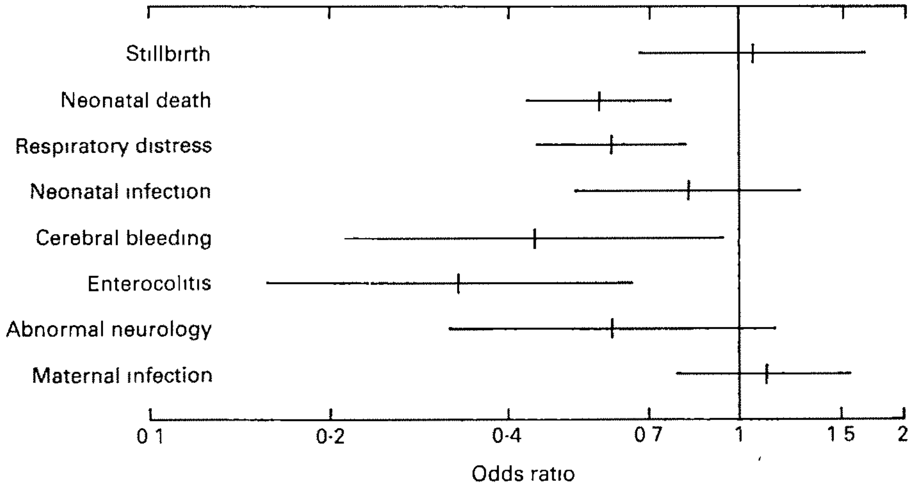


Fig. 2. Effects of corticosteroid administration before preterm delivery (typical odds ratio and 95% confidence interval).

deaths in participants who had received corticosteroids, and none among controls. All these 12 deaths were associated with proteinuria of >2 g/24 h for more than 14 days, a severity of disease that was not found in any of the placebo-treated women. The investigators recognized that this unpredicted difference may have arisen by chance, and recommended that the hypothesis it had generated should be tested in further research. Although similar numbers of hypertensive women have participated in later trials (Morrison *et al.* 1978; Collaborative Group on Antenatal Steroid Therapy 1981; Gamsu *et al.* 1989), there have been no further fetal deaths among their babies, so the hypothesis remains unsubstantiated.

The point estimate of the typical odds ratio for maternal infection is just above 1, that for fetal or neonatal infection just below 1 (Tables 7 and 8), but the 95% CI of both point estimates are quite wide. A further analysis, restricted to women with prolonged rupture of the mem-

Table 5. Effect of corticosteroids before preterm delivery on early neonatal deaths

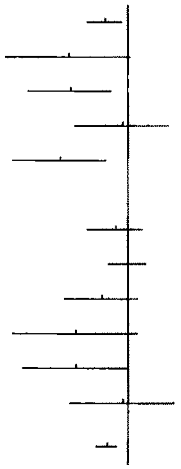
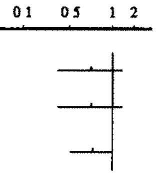
Study	Treated		Control		Odds ratios and 95% CI	
					Numerical	Graphical
	n	(%)	*n*	(%)		0 1 0 5 1 2 10
Liggins & Howie (1972)	36/532	(6 77)	60/538	(11 15)	0 58 (0 38–0 89)	
Block *et al* (1977)	1/69	(1 45)	5/61	(8 20)	0 22 (0 04–1·12)	
Schutte *et al* (1979)	3/64	(4 69)	12/58	(20 69)	0 23 (0 08–0 67)	
Taeusch *et al* (1979)	5/56	(8 93)	7/71	(9 86)	0 90 (0 27–2 96)	
Doran *et al* (1980)	2/81	(2·47)	10/63	(15·87)	0 18 (0 05–0 57)	
Teramo *et al* (1980)	0/38	(0 00)	0/42	(0 00)	1 00 (1 00–1 00)	
Gamsu *et al* (1989)	14/131	(10 69)	20/137	(14 60)	0 70 (0 34–1·44)	
Collaborative Group (1981)	36/371	(9 70)	37/372	(9 95)	0 97 (0 60–1·58)	
Morales *et al* (1986)	7/121	(5 79)	13/124	(10 48)	0·54 (0·22–1 33)	
Papageorgiou *et al* (1979)	1/71	(1·41)	5/75	(6 67)	0 27 (0 05–1 36)	
Morrison *et al.* (1978)	2/67	(2 99)	7/59	(11 86)	0 26 (0 07–1 03)	
Schmidt *et al* (1984)	5/34	(14·71)	5/31	(16·13)	0 90 (0 24–3·42)	
Typical odds ratio					0 59 (0 47–0 75)	

Table 6. Effect of corticosteroids before preterm delivery on neurological abnormality at follow-up

Study	Treated *n*	Treated (%)	Control *n*	Control (%)	Odds ratios and 95% CI: Numerical	Odds ratios and 95% CI: Graphical
MacArthur *et al* (1982)	12/139	(8·63)	15/111	(13·51)	0·60 (0·27–1·35)	
Collaborative Group (1984)	9/200	(4·50)	15/206	(7·28)	0·61 (0·27–1·38)	
Typical odds ratio					0·61 (0·34–1·08)	

branes in these 12 trials, suggests that the risk of infection may be increased or may be decreased by steroids in these circumstances, since, once again, the confidence interval is wide (typical odds ratio 1·26, 95% CI 0·66–2·40).

Secondary analysis on women with prelabour rupture of the membranes

Separate data referring to women with prelabour rupture of the membranes are available from seven trials (four from the main analysis and the three others listed in Table 2). These show that corticosteroid administration also reduces the risk of respiratory distress syndrome in these circumstances. The point estimate of a 45% reduction in the odds (typical odds ratio 0·55, 95% CI 0·40–0·75 Table 9) indicates an effect of similar magnitude to that observed among infants of all corticosteroid-treated mothers (Table 3).

The incidence of neonatal infection, albeit available for only five of these trials, was not statistically significantly higher in the corticosteroid-treated group than in the control group, but the available data (typical odds ratio 1·61, 95% CI 0·87–2·98) suggest that corticosteroid administration is more likely to increase than to decrease the occurrence of neonatal infection (Table 10).

Discussion

This overview of randomized trials of antenatal corticosteroid administration (24 mg betamethasone, 24 mg dexamethasone, or 2 g hydrocortisone) has shown that corticosteroid administration leads to statistically and clinically significant reductions in neonatal morbidity and mortality, and that these are very unlikely to be outweighed by unwanted effects of these drugs (Fig. 2). Overall, the reduction in the odds of neonatal respiratory morbidity is of the order of 40–60%. Further, the beneficial effects of antenatal corticosteroids appear to apply to babies born at all gestational ages at which respiratory distress syndrome may occur, and regardless of whether or not there has been prelabour rupture of the membranes. Although babies born >24 h and <7 days after beginning steroid administration may well benefit most from prophylaxis, the evidence suggests that babies born outside

Table 7. Effect of corticosteroids before preterm delivery on maternal infection

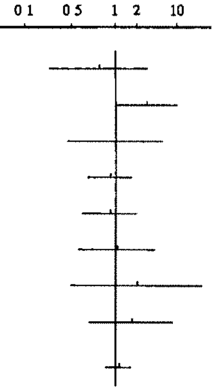
Study	Treated *n*	Treated (%)	Control *n*	Control (%)	Odds ratios and 95% CI: Numerical	Odds ratios and 95% CI: Graphical
Liggins & Howie (1972)	5/108	(4·63)	6/91	(6·59)	0·69 (0·20–2·32)	
Taeusch *et al* (1979)	14/56	(25·00)	8/71	(11·27)	2·59 (1·03–6·51)	
Gamsu *et al* (1989)	6/126	(4·76)	6/125	(4·80)	0·99 (0·31–3·16)	
Collaborative Group (1981)	27/349	(7·74)	29/347	(8·36)	0·92 (0·53–1·59)	
Morales *et al* (1986)	16/121	(13·22)	18/124	(14·52)	0·90 (0·44–1·85)	
Papageorgiou *et al* (1979)	9/71	(12·68)	9/75	(12·00)	1·06 (0·40–2·85)	
Morrison *et al* (1978)	4/67	(5·97)	2/59	(3·39)	1·76 (0·34–9·03)	
Schmidt *et al* (1984)	13/32	(40·63)	9/29	(31·03)	1·51 (0·53–4·25)	
Typical odds ratio					1·11 (0·81–1·51)	

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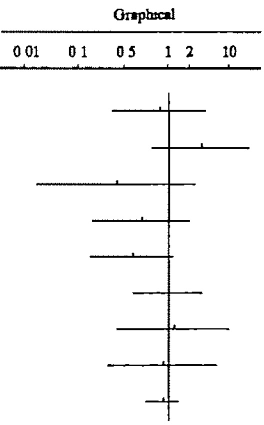
Table 8. Effect of corticosteroids before preterm delivery on fetal or neonatal infection

Study	Treated *n*	Treated (%)	Control *n*	Control (%)	Odds ratios and 95% CI: Numerical
Howie & Liggins (1977)	5/532	(0·94)	6/538	(1 12)	0 84 (0 26–2·76)
Taeusch *et al* (1979)	7/56	(12 50)	4/71	(5 63)	2 37 (0 68–8 18)
Doran *et al* (1980)	1/81	(1 23)	3/63	(4 76)	0 27 (0 04–2 01)
Gamsu *et al* (1989)	4/126	(3 17)	7/125	(5 60)	0 56 (0 17–1 88)
Collaborative Group (1981)	4/371	(1 08)	10/372	(2 69)	0 42 (0 15–1 21)
Morales *et al* (1986)	11/121	(9 09)	11/124	(8 87)	1 03 (0 43–2 46)
Papageorgiou *et al* (1979)	4/71	(5 63)	4/75	(5 33)	1 06 (0 26–4 39)
Schmidt *et al* (1984)	5/34	(14 71)	5/31	(16 13)	0 90 (0 24–3 42)
Typical odds ratio					0 83 (0 54–1·26)



this optimum period can also benefit. There is no evidence to support the view that the gender of the baby modifies these effects. Indeed, we have been unable to identify any subgroup of babies at risk of respiratory morbidity for which there are data to justify a conclusion that corticosteroids have no beneficial effects.

The clear-cut reduction in the risk of respiratory distress is, as far as we can judge from the admittedly limited data available, accompanied by reductions in periventricular haemorrhage and necrotizing enterocolitis. All of this results in a reduced early neonatal mortality rate, and reductions in the duration, and thus the costs, of hospital neonatal care.

The significant reduction in the duration of neonatal hospitalization has obvious social and economic implications. Avery (1984) has estimated that appropriate use of antenatal corticosteroids could save 35 million dollars per year in intensive care costs in the United States. Morales *et al.* (1986) reported an average saving of $17 300 per woman treated.

A number of possible short-term and long-term risks of antenatal corticosteroid administration have been considered (Taeusch 1975). The immunosuppressive effects of corticosteroids could result in an increased susceptibility to fetal, neonatal or maternal infection, or to a delay in its recognition. Over the 11 years following the introduction of corticosteroids for fetal lung maturation in England and Wales, there were two maternal deaths from septicaemia associated with their use (Department of Health and Social Security 1979, 1982, 1986, 1989). It is these two deaths that underlie the opposition of some British obstetricians to the use of corticosteroids for fetal lung maturation.

In the presence of intact membranes, there is no clear evidence of an increase in the risk of

Table 9. Effect of corticosteroids after prelabour rupture of the membranes on respiratory distress

Study	Treated *n*	Treated (%)	Control *n*	Control (%)	Odds ratios and 95% CI: Numerical
Block *et al* (1977)	3/25	(12 00)	5/26	(19 23)	0 59 (0 13–2 61)
Morales *et al* (1986)	30/121	(24 79)	63/124	(50 81)	0 33 (0 20–0 56)
Collaborative Group (1981)	15/153	(9 80)	17/135	(12 59)	0 75 (0 36–1 57)
Nelson *et al* (1985)	10/22	(45 45)	11/22	(50 00)	0 84 (0 26–2 70)
Schmidt *et al* (1984)	7/24	(29 17)	6/17	(35·29)	0 76 (0 20–2 84)
Garite *et al* (1981)	14/80	(17 50)	17/79	(21·52)	0 78 (0 35–1 70)
Iams *et al* (1985)	10/38	(26 32)	12/35	(34 29)	0 69 (0 25–1 86)
Typical odds ratio					0 55 (0 40–0 75)

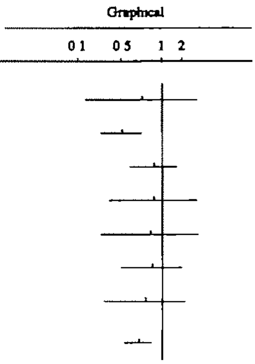
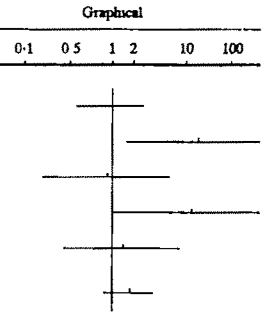


Table 10. Effect of corticosteroids after prelabour rupture of the membranes on neonatal infection

Study	Treated *n*	Treated (%)	Control *n*	Control (%)	Odds ratios and 95% CI: Numerical
Morales *et al* (1986)	11/121	(9·09)	11/124	(8·87)	1·03 (0·43–2·46)
Nelson *et al* (1985)	5/22	(22·73)	0/22	(0·00)	9·07 (1·44–57·16)
Schmidt *et al* (1984)	4/24	(16·67)	3/17	(17·65)	0·93 (0·18–4·78)
Garite *et al* (1981)	4/80	(5·00)	0/79	(0·00)	7·58 (1·05–54·87)
Iams *et al* (1985)	4/38	(10·53)	3/35	(8·57)	1·25 (0·27–5·88)
Typical odds ratio					1·61 (0·87–2·98)



maternal, fetal or neonatal infection. In the presence of prolonged rupture of the membranes, the absolute risk of fetal and neonatal infection may be greater, but again, controlled trials provide no strong evidence that corticosteroids increase this risk. Follow-up data from the Dutch trial (Smolders-de Haas *et al.* 1990) suggest that there may be an increased occurrence of pharyngeal and ear infections in infancy among infants in the corticosteroid group during the first 2 years of life. Similar data from other follow-up studies are needed to establish whether or not this is a consistent finding.

Instances of pulmonary oedema have been reported in pregnant women receiving a combination of corticosteroids and tocolytic drugs (Stubblefield & Kitzmiller 1980). Here again, the trials provide little in the way of information to assess the extent to which corticosteroids, *per se*, may be responsible for this serious condition. In the trial reported by Morales *et al.* (1986), pulmonary oedema occurred in two women among 44 women treated with magnesium sulphate and corticosteroids. Pulmonary oedema was not reported by the authors of the other randomized trials, so the magnitude of this risk cannot be estimated with any confidence from these data.

There is no evidence that antenatal corticosteroid administration increases the overall risk of stillbirth. The higher risk of fetal death in pregnancies complicated by hypertension noted in one trial (Liggins & Howie 1972) may reflect chance. Alternatively, it may reflect undue delay in delivering women with severe proteinuric hypertension, an explanation that is supported by the fact that no such risk was recorded in the other trials that included hypertensive women. However, the possibility that corticosteroid administration may have a specific adverse effect on the evolution of pre-eclampsia cannot be excluded using the available data.

It is important to recognize that neonatal respiratory distress syndrome is common in infants of mothers with pre-eclampsia delivered preterm: for example, it affected 36% of babies of women with pregnancy-induced hypertension in the placebo arm of the Collaborative Group trial (Schneider *et al.* 1988). In the light of the available data, it would seem reasonable to use corticosteroids to reduce this considerable neonatal morbidity, provided the commitment to early delivery implied by corticosteroid treatment is carried through. Those obstetricians who remain uncertain that the demonstrable advantages of this policy would be outweighed by possible disadvantages in hypertensive women, or in other circumstances, should collaborate in further randomized trials to provide evidence on which to base their practice more firmly.

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Structural cardiac abnormalities in the fetus: reliability of prenatal diagnosis and outcome

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Summary. The outcomes of 129 pregnancies in which the fetus was found to have a structural cardiac abnormality are reviewed. Over a 30-month period from January 1985 to June 1987, 1924 patients were referred to the British Heart Foundation Research Centre for Perinatal Cardiology at Guy's Hospital for fetal cardiac scanning. A total of 129 structural cardiac abnormalities was diagnosed; 53% of these patients were referred because of an abnormal 'four-chamber view' on ultrasound at the referring hospital; 47 of the pregnancies (69% of the 68 patients referred before 28 weeks) were terminated, and in the remaining 82 pregnancies outcome was poor with only 20 infants (16%) surviving longer than 11 months. The prenatal diagnosis was fully or partly correct in 96% of the 111 cases where it was possible to verify the diagnosis by post-mortem or postnatal diagnosis. In the 82 pregnancies not terminated, 13 of the 22 cases given a moderate or good prognosis survived more than 11 months (59% survival), but only seven of the 60 (12% survival) given a fatal, poor or uncertain prognosis. The benefits of a multidisciplinary approach are discussed.

Structural cardiac defects account for 20% of the perinatal deaths due to congenital malformations (Young & Clarke 1987) and more than half the deaths in childhood from lethal malformations (Keith *et al.* 1978). The overall frequency of congenital heart disease is eight abnormalities per 1000 pregnancies (Mitchell *et al.* 1971) of which four per 1000 are minor or easily correctable surgically Technological advances in ultrasound instrumentation and the introduction of the 'four-chamber view' (Allan *et al.* 1986) of the heart into routine prenatal anomaly scanning have improved our ability to detect fetal structural cardiac defects and should detect the most severe abnormalities (two per 1000 pregnancies (Allan *et al.* 1986)). The rarity of these defects and the need for accurate diagnosis have led to the development of referral centres specializing in fetal echocardiography. To be effective, these centres should provide the correct diagnosis, a definite prognosis and appropriate advice on further management. Although there is an extensive literature on the screening, diagnosis and management of structural cardiac defects in the fetus, there are few reports on the outcome

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of a series of pregnancies in which fetal structural cardiac abnormalities were diagnosed

The British Heart Foundation Research Centre for Perinatal Cardiology was established at Guy's Hospital, London, in 1980 and has developed into a supra-regional referral centre for the diagnosis and management of fetal structural cardiac abnormalities. This paper reports on the outcome of 129 pregnancies in which cardiac abnormalities were diagnosed by the Centre and relates the outcome of the pregnancy to the prognosis given at the time of the initial prenatal diagnosis.

Subjects and methods

Pregnant women referred at their obstetrician's discretion from the South of England and Wales over a 30-month period from 1 January 1985 to 30 June 1987 were included in the study. Indications for referral were: (i) a strong family history, i e. the woman, her partner or a previous child to either partner had had a structural cardiac abnormality; (ii) an abnormal four-chamber view; (iii) an extracardiac abnormality; (iv) non-immune hydrops fetalis; (v) a fetal heart arrhythmia, either bradycardia or tachycardia; and (vi) other conditions where there was an increased risk of cardiac abnormality, e.g. diabetes, lithium therapy. Personal data were recorded for each woman and the fetal heart was examined with a duplex ultrasound scanner (Hewlett Packard 77020 AC) using a 3·5 MHz or 5 MHz transducer (for a recent review see Allan 1988). When a structural abnormality was detected, a diagnosis was made and a prognosis given. After counselling, the woman returned to the referring consultant for further care unless it was felt that the fetus would benefit from ongoing combined cardiological/obstetric management, in which case, management was continued at Guy's Hospital with the referring consultant's consent.

The progress and outcome of each pregnancy (including those where no abnormality was detected) were followed up and, where appropriate, post-mortems performed when parental consent could be obtained. In the majority of post-mortem cases the heart was examined at Guy's Hospital. These data have been collated for the purposes of this report.

Results

Of the 1924 pregnancies referred over this time, 129 were found to have fetuses with structural cardiac abnormalities. The average age of the women was 26·5 years (range 15–39) and 43 (34%) were nulliparous.

The reasons for the referral of the women in whom fetal structural cardiac abnormalities were diagnosed are given in Table 1. The referring consultant's letter was used to place the referral into one of the six categories listed in the table. The commonest reason for referral in this affected group was a cardiac abnormality detected at routine ultrasound scan (abnormal four-chamber view) and 53% of abnormal pregnancies were referred for this reason; the frequency of this indication for referral has risen over the study period.

A wide range of prenatal diagnoses was made. Of the 129 affected fetuses 69 (53%) had a single abnormality and the remainder had multiple cardiac abnormalities Table 2 lists the prenatal diagnoses made with ultrasound. In order to simplify classification for Table 2, those fetuses with multiple cardiac abnormalities were classified according to the most significant abnormality or in the 'other' category if this was not possible (7 fetuses).

Chromosomal analysis was performed on 51 of the 129 fetuses either prenatally (41) or at post-mortem (10); 27 (21%) had an abnormal karyotype and four cultures failed. Trisomy 21 was found in 11 (41% of abnormal karyotypes), trisomy 18 in 6 (22%) and Turner's syndrome (XO) in four fetuses (15%). Of the 25 pregnancies in which a chromosomal abnormality was diagnosed prenatally, 13 were terminated.

Decisions on further management after diagnosis involved the parents, the referring consultant and the Centre. Table 3 shows the management decisions made for the 129 pregnancies. Of the 68 women referred before 28 weeks gestation, 47 (69%) had their pregnancies terminated. Of the remaining pregnancies not terminated, 37 women (29% of 129) began labour spontaneously, 15 (12%) of them preterm (<37 weeks). Information was not available for one woman.

The overall perinatal and neonatal outcome was poor and is shown in Table 4. Of the 82 pregnancies not terminated, 23 infants (18% of total 129 pregnancies) were stillborn and 59 (46%) were liveborn, but only 20 (16%) of these infants survived more than 11 months. Eleven months is the latest infant death with a follow-up of 18–42 months to the end of 1988.

Table 1. The reasons for referral to the Perinatal Cardiology Centre at Guy's Hospital of 129 pregnant women in whom fetal structural cardiac abnormalities were subsequently diagnosed.

Reasons for referral	*n*	(%)
Abnormal four-chamber view	68	(53)
Family history	26	(20)
Extracardiac abnormality	17	(13)
Non-immune hydrops	10	(8)
Arrhythmia	5	(4)
Other	3	(2)
Total	129	(100)

Of the 109 fetuses who did not survive pregnancy or longer than 11 months postnatally, 91 (83%) had a post-mortem including 44 of the 47 (94%) terminations of pregnancy. In the remaining 18 fetuses who did not have a post-mortem, verification of the prenatal ultrasonographic diagnosis was not possible. In the 20 survivors, the diagnosis was confirmed by postnatal echocardiography or cardiac catheterization before surgery. The predicted structural abnormality was correct in 90 fetuses (81% of 111), partly correct in 17 (15%), and incorrect in four. In the four fetuses in which the structural defect was incorrectly diagnosed, two were given a good prognosis and are alive and well. The other two were given a poor prognosis and both had fatal cardiac abnormalities—one was terminated and the other died at 3 months of age.

In the 1924 pregnant women referred over the study period, 26 fetal cardiac abnormalities were not diagnosed; 15 were minor abnormalities (VSD or ASD) and only one of these infants has not survived. Eleven major abnormalities were undiagnosed: two had an inadequate examination because of maternal obesity; three had coarctation of the aorta; two had total anomalous pulmonary venous drainage; two had severe pulmonary stenosis; and the remaining four had supravalvular aortic stenosis, tetralogy of Fallot, transposition of the great arteries and an abnormal origin of the pulmonary artery, respectively. Four of these infants have not survived, all but one because of complications following corrective surgery.

Table 2. Ultrasound diagnoses in 129 fetuses with structural cardiac abnormalities.

Prenatal ultrasound diagnosis	*n*	(%)
Atrioventricular septal defect	22	(17)
Coarctation of the aorta	15	(12)
Ventricular septal defect	12	(9)
Hypoplastic left heart	10	(8)
Pulmonary atresia	8	(6)
Double outlet right ventricle	7	(5)
Other	54	(42)
Total	129	(100)

Assuming that there were two false positive (incorrect diagnoses were made on a further two fetuses but both had fatal cardiac abnormalities), the sensitivity and specificity of the prenatal diagnosis were 83·6% and 99·9%, respectively. The positive predictive value was 98·4% and the negative predictive value 98·6%.

A comparison of the outcome of the pregnancy and the prognosis given at the time of diagnosis is summarized in Table 5 for the 82 pregnancies not terminated. Further analysis of the subgroup of pregnancies referred before 28 weeks and not terminated is included to demonstrate that the outcome of this subgroup is similar to that of the group as a whole.

Discussion

The diagnoses made prenatally at this Centre were fully or partly correct for 96% of the fetuses, and the prognoses based on these diagnoses were accurate and could be reliably used in the subsequent management. Overall, 26 abnormalities were not diagnosed of which 15 were minor and only five of the 26 infants have not survived: four of the five as a result of complications following surgery. Overall the perinatal outcome was poor. Of the 82 pregnancies not terminated, 60 were given a prognosis of fatal, poor, or uncertain. In this group, only seven infants survived more than 11 months, a survival rate of 12%. No distinction is made in

Table 3. The management decisions made after initial ultrasound diagnosis in the 129 pregnancies in which fetal structural cardiac defects were diagnosed.

Management decisions	*n*	(%)
Termination	47	(36)
Spontaneous labour	37	(29)
Induction of labour	31	(24)
Intrauterine death	13	(10)
No follow-up	1	(1)
Total	129	(100)

Table 4. Outcome in 129 pregnancies with prenatal diagnoses of fetal structural cardiac abnormalities.

Outcome	*n*	(%)
Terminations	47	(36)
Stillbirths	23	(18)
Livebirths*	59	(46)
Total	129	(100)

* 27 babies died within 1 month, 12 died within 11 months and 20 (16%) survive

this report between short-term and long-term prognosis, and the quality of life for these seven infants is poor and several are expected to die in early childhood. These figures contrast with the outcome of the 22 pregnancies given a moderate or good prognosis where 13 infants have survived more than 11 months—a survival rate of 59%. In the subgroup of patients who were referred before 28 weeks and not terminated, the results were similar, suggesting that the diagnosis and prognosis are reliable at these earlier gestations.

Increasing numbers of pregnant women are being referred because of an abnormal four-chamber view on routine fetal anomaly scanning at 16–18 weeks gestation. This reflects increasing awareness of the importance and accuracy of this screening method to detect fetal structural cardiac abnormalities. Our results provide further support for the inclusion of this technique in the teaching of those involved in fetal anomaly screening.

A high rate of abnormal karyotypes in fetuses with structural cardiac abnormalities has been reported before. In this series, 27 (21%) of the total 129 fetuses had abnormal karyotypes compared with the reported rate of 5% (Copel *et al.* 1986). Karyotyping was not routinely performed on these fetuses but was recommended where: (i) a particular cardiac malformation is associated with an abnormal karyotype, such as atrioventricular canal defects with trisomy 21; or (ii) the appearance of the fetus at post-mortem suggested an abnormal karyotype. Because the true frequency of abnormal karyotypes became apparent during the study period, karyotyping is now performed prenatally in all those pregnancies referred at suitable gestations in whom a fetal structural cardiac abnormality is diagnosed. Cordocentesis is a safe and rapid method of obtaining blood for karyotyping and is being used more frequently.

Pregnant women are selected for ongoing management at Guy's Hospital if continued care may improve the outcome of the pregnancy, for instance, those in whom maternal medication is used to treat the fetus, those in whom regular scanning is used to determine the optimum time for intervention, or those where early surgical correction is anticipated. Guy's Hospital is one of the few hospitals in the country where combined obstetric and paediatric cardiosurgical services are available.

Labour is usually induced in these pregnancies at 38–39 weeks so that paediatric cardiological and surgical services can be prepared. However, of the 69 pregnancies in this study in which the fetus was alive at the onset of labour, 15 (22%) were delivered spontaneously before 37 weeks. This contrasts with the rate of preterm delivery in singleton pregnancies in the general population of 6% (Anderson 1981). Caesarean section is undertaken for obstetric reasons, the fetal cardiac status rarely being an indication. Fetal distress in labour is managed according to the prognosis of the cardiac lesion and fetuses with a poor prognosis are not monitored in labour

Concern has been expressed regarding advice given by obstetricians on outcome and future paediatric management in areas where they have little or no experience (MacKinnon 1987). The

Table 5. Prenatal prognosis compared with the eventual outcome in 82 pregnancies allowed to continue*.

	Overall			Referred at <28 weeks	
Prognosis given	*n*	(%)	No. survived	*n*	No. survived
Fatal	13	(16)	0	3	0
Poor	40	(49)	6	6	2
Uncertain	7	(9)	1	4	0
Moderate/good	22	(27)	13	8	5
Total	82	(101)	20	21	7

*The overall number of pregnancies and those referred at <28 weeks gestation and not terminated are detailed.

work forming the basis of this paper illustrates an approach to the management of complex, rare fetal abnormalities which involves co-operation between obstetricians and other disciplines. This requires frequent communication and regular meetings attended by the obstetric, neonatal, paediatric cardiological and cardiosurgical medical staff, and representatives of the midwifery and neonatal nursing staff who will be involved in ongoing care.

Accurate prenatal diagnosis and assessment of prognosis have meant reassurance for those parents where an abnormality has been excluded or a good prognosis given. Pregnancies referred before 28 weeks gestation could be terminated on the basis of accurate information and unnecessary caesarean sections for fetal distress avoided where the abnormality was diagnosed too late to terminate the pregnancy. Those where close ultrasound monitoring through pregnancy was felt to be necessary or early surgical intervention was anticipated could be selected and managed by a team with obstetric, cardiological and cardiosurgical expertise.

The rarity and complexity of fetal structural cardiac abnormalities mean that most obstetricians will gain little experience in the diagnosis and management of these abnormalities and their role will be the referral of 'at-risk patients' for fetal echocardiography. The results reviewed in this report confirm that referrals to this Centre will be accurately assessed and appropriately managed.

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Child outcome following mid-trimester amniocentesis: development, behaviour, and physical status at age 4 years

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Summary. Four-year-old children whose mothers had mid-trimester amniocentesis ($n = 88$) were compared with children whose mothers chose not to have the procedure ($n = 46$). Intelligence, visual-motor-perceptual skills, language, behaviour, social competence, temperament, physical growth, hearing, and middle-ear function were measured using standardized procedures. Health histories were obtained by maternal report. The results suggest that the wide range of developmental and behavioural variables studied is not influenced by removal of amniotic fluid in the mid-trimester. However, mothers who had amniocentesis were more likely to report a history of ear infections in their child ($P = 0{\cdot}04$). In support of this finding were the results of audiological assessment which demonstrated a trend toward a higher rate of bilateral middle-ear impedance abnormalities in children whose mothers had amniocentesis ($P = 0{\cdot}06$). Further study of the upper respiratory system is recommended to explore potential long-term sequelae of mid-trimester amniocentesis.

Mid-trimester genetic amniocentesis is generally regarded as 'safe', although it increases the risk of fetal loss (Lowe *et al.* 1978; Medical Research Council 1977; NICHD National Registry for Amniocentesis Study Group 1976; Porreco *et al.* 1982; Report to the Medical Research Council 1978; Tabor *et al* 1986), may negatively affect the respiratory system (Hislop & Fairweather 1982; Report to the Medical Research Council 1978; Tabor *et al.* 1986; Vyas *et al* 1982), and may increase the risk for orthopaedic abnormalities (Cruikshank *et al.* 1983; NICHD 1976; Report to the Medical Research Council 1978; Wald *et al.* 1983). Because factors that increase the risk of fetal mortality may be assumed to increase the risk of morbidity (Prechtl 1967), infants and children whose mothers had amniocentesis may be regarded as 'at-risk' until proven otherwise.

Studies of children's development subsequent to amniocentesis appear to be motivated by a concern that removal of a portion of the

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amniotic fluid may somehow compromise the developing brain, although potential mechanisms for influences on the central nervous system have not been proposed. Investigations of potential developmental sequelae have not shown deficits in infant developmental status, leading to the view that amniocentesis has no long-term consequences (Lowe *et al.* 1978; NICHD 1976, Report to the Medical Research Council 1978; Howard & Crandall 1979). Conclusions about the safety of amniocentesis, however, must be limited to the age range of children studied. Only a narrow range of behaviours can be assessed in infants, therefore complete reassurance regarding safety is not provided by studies showing that early development is normal. Impairments may not become evident until language, perception and other complex symbolic intellectual activities may be assessed (Hunt 1979; Gillberg *et al.* 1982).

In our longitudinal study, children were assessed at 4 days, 6 months, and 4 and 7 years. The findings from the neonatal and 6-month examinations did not reveal any negative consequences for neonatal neurobehavioural status (Finegan *et al.* 1984), mental or motor development, or temperament (Finegan *et al.* 1985). Examination of physical status showed that growth did not appear to be affected, but 5% of the children had skin marks caused by the needle.

In this report, we present findings from the assessment of intelligence, visual-motor co-ordination and perception, language, behaviour, social competence, temperament, physical growth, and health at age 4 years. Because both genetic and environmental factors influence development, it was important to assess the potential influence of these variables on child outcome. Consequently, maternal intelligence, quality of the home environment, maternal expectations for child achievement, and attitudes toward child-rearing were assessed Hearing and middle-ear function also were examined because fetal middle-ear and eustachian tube structures are developing in the mid-trimester (Maue-Dickson 1981). Accordingly, we were concerned that these structures may be affected by exposure to ultrasonic energy or the changes resulting from amniotic fluid removal.

Subjects and methods

Women in the study were recruited from late 1980 to early 1982 from the antenatal genetic clinic at the Toronto General Hospital. Referrals to the clinic were screened for women between 35 and 40 years of age who were at risk for fetal chromosome abnormality because of their age. On average, amniocentesis was undertaken at 16·4 weeks (SD 0·83, range 15–20), and 20·4 ml (SD 2·57, range 13–27) of amniotic fluid were removed for chromosome studies. The women who participated in the control group also were eligible for amniocentesis because of their age, but they chose not to have the test because they feared the risks (60%), because of their feelings about selective termination of pregnancy (29%), or for a variety of other reasons (11%).

The experimental group consisted of 100 women and the control group consisted of 56 women. The numbers in each group represented similar rates of agreement to participate among women invited into the study (84% and 83·6%, respectively) The women in each group were similar in gestational age at entry to the study so that the possibility that one group favoured continuing pregnancies is ruled out.

The groups did not differ in age of the child at follow-up (overall mean 4·16 years, SD 0·16). Nevertheless, the effects of age were controlled in the comparisons of physical growth indices by using analysis of covariance (ANCOVA) Control for age was unnecessary for the psychological and behavioural measures because the norms are standardized by age. The groups did not differ in sex distribution or birth order: 50% of the children were female, and 35% were first-born. Moreover, the groups did not differ on a wide range of pre-, peri- and neonatal variables that potentially could influence development including exposure to anaesthetic drugs, method of delivery, obstetric complications, gestational age at birth, growth variables, or bilirubin levels (see Finegan *et al* 1984).

Follow-up rates

Sample attrition from study entry to 4-year follow-up is presented in Table 1. Annual contact is maintained by sending each child a birthday card with a change of address card enclosed. The subject attrition rate has been extremely low. In the present sample there are 88 children whose mothers had amniocentesis and 46 children in the control group.

Procedures

The children and their mothers were assessed in

Table 1. Sample attrition from entry to study to follow-up at age 4 years

Study phase	Amniocentesis group	Control group
Invited to participate	120	66
Agreed to participate	101 (84·2%)	55 (83·3%)
Withdrew/lost before neonatal follow-up	2	0
Study sample	99	55
Fetal deaths	3	1
Liveborn infants	96	54
Neonatal deaths	2	0
Infants to follow*	94	54
Withdrew/lost before 6-month follow-up	3	2
Infants in 6-month follow-up	91 (96·8%)	52 (96·3%)
Four-year follow-up		
Withdrew/moved before 4-year follow-up	4	6
Returned before 4-year follow-up	1	0
Four-year-olds followed	88 (93·6%)	46 (85·2%)

* Attrition rates for 6-month and 4-year follow-up studies are based on number of children available for study (i.e. number of infants who survived beyond the neonatal period)

the department of psychology at the Hospital for Sick Children, Toronto. Parents signed consent forms approved by the Human Subjects Review Committee. Psychological and audiological examinations were administered by experienced individuals who did not know which mothers had had amniocentesis.

Assessment of child intelligence, cognitive abilities, and behaviour

The child's level of intelligence was assessed with the scales developed by McCarthy (1972) which yield a measure of general intellectual ability. Subtests provide measures of competence on the following scales: verbal, perceptual-performance, quantitative, memory, and motor. Scores are stable over repeated testings and are highly correlated with full-scale IQ scores derived from both the Wechsler Preschool and Primary Scale of Intelligence and the Stanford–Binet (McCarthy 1972).

Fine motor co-ordination was assessed with the Eye-Motor Co-ordination subtest described by Frostig *et al.* (1966). This task requires the child to draw continuous straight, curved, or angled lines between boundaries of various widths. Norms are available and test–retest reliability over 2 weeks is high. Visual perception was assessed with the test developed by Beery (1982), in which the child is asked to copy a series of geometric forms arranged in increasing order of difficulty.

Language comprehension and expression were assessed by the scales devised by Reynell (1977). The test has been standardized on a large sample of British children.

Hyperactivity and activity levels were assessed by parent report questionnaires. Mothers completed the abbreviated rating scale developed by Conners (1973), a 10-item checklist in which symptomatic behaviours (e.g. 'excitable', 'impulsive', 'constantly fidgeting') are scored on a 4-point scale. Mothers also completed the Werry–Weiss–Peters Activity Scale (Werry 1968), a 22-item checklist describing restless, fidgety, and active behaviours in various situations.

The Child Behaviour Checklist (CBCL) is an objective and comprehensive means for reporting behaviour problems and level of social competence of children from 4 to 16 years of age (Achenbach & Edelbrock 1983). The checklist was completed by mothers to identify children with internalizing (e.g. social withdrawal, depression, immaturity, etc) and/or externalizing (e.g. aggression, delinquency, etc.) behaviour problems. The CBCL also includes items on social, school, and activity-related behaviours to comprise a measure of socially competent behaviour.

Because 'difficult' temperament (i.e. crying, whining, irritability) may be associated with perinatal risk factors (Bates 1985), the children's temperament was assessed using the Preschool Characteristics Questionnaire (Finegan *et al.* 1989) which requires mothers to rate temperament characteristics on a 7-point scale.

Background characteristics

Because group differences in outcome may arise from differences in family background rather than as a result of amniocentesis, parent and family characteristics were measured.

A. B. Hollingshead's *Four Factor Index of Social Status* (available from author, Sociology Dept, Yale University, 140 Prospect St, New Haven, CT 16520, USA) was used to assess socio-economic status based on level of education and occupation of both parents. Maternal intelligence was assessed with a short form of the Wechsler Adult Intelligence Scale (Wechsler 1981). The 'information, similarities, and block design' subtests were administered. Together, they correlate 0·94 with full-scale IQ (Matarazzo 1972). A questionnaire was developed to assess various aspects of level of stimulation in the home based on a questionnaire (HOME) described by Caldwell & Bradley (1984). The questionnaire elicited information on the provision of stimulation, such as the types of toys available, academic experiences, etc., as well as the expectations held for socially mature behaviour. Using an independent sample, a modest but significant correlation was observed between questionnaire scores and scores obtained from the complete HOME interview version, $r(33) = 0{\cdot}48, P<0{\cdot}01$.

Parents' achievement motivation for their child was assessed using a modified version of the Parental Development Timetable devised by Touliotis & Bedeian (1982). This questionnaire provides information on maternal expectations for independence and achievement. Parental authoritarianism–permissiveness was assessed with the scale developed by Ernhart & Loevinger (1969). This questionnaire elicits information on parental beliefs, demand for respect by children, and the rights of parents to intrude on the lives of their children.

Assessment of physical growth, health and hearing

Height, weight, and occipital–frontal head circumference were measured using standard procedures (Smith 1982). The child's health history was obtained by maternal report on a questionnaire but the children were not examined physically. Mothers reported on their child's history of respiratory illnesses and hospitalizations and whether their child had ever been examined or treated by an orthopaedic specialist. Medical records were examined when there was an indication of illness or hospitalization.

Children underwent an audiological assessment in the department of audiology by individuals blind to the children's group. The battery included pure-tone and speech reception thresholds, as well as impedance audiometry. Pure-tone and speech reception thresholds were determined using a Grason-Stadler GSI 16 audiometer with TDH-39 headphones. Middle-ear function was assessed using a Madsen Z073 impedance bridge. Equipment is calibrated every 4 months according to departmental standards.

Results

Background characteristics

Mothers of children in this study, on average, were well educated and from the upper social classes. Group differences were not observed in social status (overall mean 50·3, SD 11·1). Over 90% of the children in both groups lived in intact, two-parent families with similar rates of working mothers. The groups were similar in the proportion of women who smoked cigarettes and who reported moderate to heavy alcohol consumption during the index pregnancy. Mothers who had amniocentesis did not differ from those in the control group on measures of maternal IQ (overall mean 107·6, SD 16·0), home environmental quality, child-rearing style, or maternal attitudes toward and expectations for child achievement or independence. Thus, the background characteristics of the two groups did not differ except on one variable: mothers who had had amniocentesis and were participating in the 4-year follow-up were, on average, 8 months older than mothers of children in the control group (mean 41·6 years, SD 1·61 and mean 40·9 years, SD 1·37, respectively, $t(131) = 2{\cdot}40, P<0{\cdot}05$).

Developmental and behavioural outcome

Group means and standard deviations for measures of intelligence, cognitive abilities and behaviour are presented in Table 2 Significant group differences were not observed for any of these outcome variables.

Physical growth and health

The groups did not differ significantly on phys-

Table 2. Measures of intelligence, visual motor-perception, language, and behaviour for children of mothers who had amniocentesis and control group children

Measure of ability	Amniocentesis group Mean	Amniocentesis group (SD)	Control group Mean	Control group (SD)
Intelligence				
General cognitive index	115·7	(13·1)	117·3	(15·0)
Verbal	57·7	(9·0)	57·8	(10·0)
Perceptual-performance	59·7	(6·8)	60·7	(6·7)
Quantitative	58·4	(9·0)	60·9	(9·5)
Memory	56·1	(9·6)	57·7	(9·8)
Motor	51·4	(6·3)	50·8	(6·7)
Visual-motor-perception				
Visual-motor co-ordination	10·9	(1·5)	11·1	(1·6)
Age equivalence (years)	4·4	(0·6)	4·6	(0·7)
Visual-perceptual integration	10·7	(2·3)	10·7	(2·3)
Age equivalence (years)	4·1	(0·9)	4·1	(0·9)
Language (standard scores)				
Verbal comprehension	1·0	(0·6)	1·0	(0·6)
Age equivalence (years)	5·0	(0·6)	5·0	(0·6)
Language production	0·7	(0·8)	0·7	(0·6)
Age equivalence (years)	4·1	(0·8)	4·1	(0·6)
Behaviour				
Hyperactivity index*	5·8	(3·9)	5·2	(3·6)
Activity level*	10·8	(5·1)	10·1	(5·3)
Behaviour problems*				
Sum T-score	51·3	(9·2)	50·5	(12·2)
Internalizing T-score	50·4	(9·5)	51·1	(12·0)
Externalizing T-score	50·0	(8·4)	48·7	(10·7)
Social competence				
Sum T-score	47·7	(12·7)	50·1	(11·2)
Activities	46·4	(9·7)	48·8	(7·1)
Social participation	46·0	(8·4)	47·1	(9·5)
Difficult temperament (raw score*)	28·2	(7·2)	26·8	(6·1)

Data on two children whose mothers had amniocentesis were excluded: scores for intelligence, visual-motor-perception, and language were not included for a child with a Pervasive Developmental Disorder because of questionable validity (General Cognitive Index = 62). Intelligence and language scores for a non-English-speaking child also were excluded. Information on behaviour for these children was obtained via parental report and was retained in the above analyses.

* Lower scores are optimal

ical growth variables (Table 3). Mothers in both groups gave similar ratings of their child's health: significant differences were not found in the number of hospitalizations, the rates of respiratory problems, or the need for consultation with or treatment by an orthopaedic specialist.

Ear infections, middle-ear function, and hearing

Mothers who had amniocentesis were more likely to report that their child had ear infections than were mothers in the control group $\chi^2(1) = 4{\cdot}42$, $P<0{\cdot}04$; Table 3). Converging with this parent report data, blind assessment of audiological status demonstrated a trend toward a higher rate of bilateral middle-ear impedance abnormalities in children whose mothers had amniocentesis ($\gamma^2(1) = 3{\cdot}41$, $P = 0{\cdot}06$). Although some children with ear infections were those with bilateral middle-ear impedance abnormalities, these problems did not necessarily co-exist. Group differences were not observed in rates of hearing loss (Table 4). Moderate unilateral hearing loss in one child of a mother who had amniocentesis resolved following surgery for cholesteatoma.

Known associations with ear infections such as school or day-care attendance, exposure to siblings, season of birth, and idiosyncratic diagnos-

Table 3. Physical growth and health history of children whose mothers had amniocentesis and control group children

Variable	Amniocentesis group* (n = 88)		Control group* (n = 46)	
	Mean	(SD)	Mean	(SD)
Growth				
Height (cm)	105·7	(4·4)	105·0	(3·3)
Weight (kg)	17·8	(2·9)	18·2	(2·8)
Head circumference (cm)	51·5	(1·3)	51·5	(1·4)
Maternal rating of child health†	1·4	(0·7)	1·3	(0·6)
	n	(%)	n	(%)
Health history				
Orthopaedic consult/treatment	4‡	(4·6)	2	(4·3)
Number of children with respiratory illnesses	28	(31·8)	9	(19·6)
Types of respiratory illness§				
Pneumonia	4		3	
Bronchitis	15		5	
Wheezing	14		4	
Asthma	4		2	
Croup	1		1	
Other‖	4		2	
Number of children hospitalized for respiratory illnesses	9	(10·2)	3¶	(6·5)
With ear infections**	64††	(75·3)	26¶	(57·8)
With myringotomies/tubes	5††	(5·9)	2¶	(4·4)

* Group differences in growth and maternal rating of child health were tested using t-tests Group differences in health history variables were tested using χ^2.

† Mothers rated their child's health status on a 5-point scale (5 = poor, 3 = average, 1 = excellent).

‡ Data available on 87 children

§ Percentages are not calculated because the illnesses are not independent.

‖ Other respiratory illnesses include persistent cough, frequent URI, transient tachypnoea.

¶ Data available on 45 children

** Significant group difference, $P = 0·04$

†† Data available on 85 children

tic patterns associated with a particular type of medical care (i.e. care by paediatrician, family physician, or general practitioner) were unrelated to maternally-reported history of ear infections. Factors related to the amniocentesis procedure, such as the amount of amniotic fluid withdrawn or the gestational age at amniocentesis, did not differ in children with or without ear infections or impedance abnormalities Season of testing did not account for the group differences in bilateral impedance abnormalities in children. Ultrasound exposure was not associated with ear infections or bilateral impedance abnormalities.

Discussion

Children whose mothers had mid-trimester amniocentesis for risks related to maternal age did not differ in intelligence, cognition, language, behaviour, temperament, social competence, physical growth, or respiratory or orthopaedic status, in comparison with children whose mothers did not undergo this procedure. The present study failed to reveal adverse effects of amniocentesis on cognition and behaviour in the preschool period, and, in fact, the results suggested that the children in this sample are doing very well. Their level of general cognitive ability was 1 SD above the normative mean, highlighting the need to use well-matched control groups in studies of the risks of various prenatal diagnostic techniques.

Despite these reassuring findings, it is premature to conclude that amniocentesis is entirely free of risk. Mothers who had amniocentesis were more likely to report a history of ear infections in their child. Data obtained by maternal report may have many sources of error. The most obvious are those arising from

Table 4. Hearing and middle-ear function in children whose mothers had amniocentesis and control group children

	Amniocentesis group		Control group	
	n	(%)	*n*	(%)
Hearing loss				
Ears tested	162		88	
Normal	149	(92·0)	83	(94·3)
Mild (26–40 dB nHL)	12	(7·4)	5	(5·7)
Moderate (41–55 dB nHL)	1	(0·6)	—	—
Moderately severe (56–70 dB nHL)	—	—	—	—
Impedance abnormalities				
Children tested	82		44	
Unilateral	6	(7·5)	4	(9·0)
Bilateral	13	(15·8)*	2	(4·5)

Criteria for abnormal middle-ear function were a middle-ear pressure value outside the paediatric range (+50 to −150 mm H_2O) and/or a compliance greater than 1·2 cc Classification of 'abnormal' impedance was made by the chief audiologist (M.B.) based on a comprehensive evaluation of all audiometric test findings (i.e. puretone and speech reception thresholds and/or impedance) The data from an intubated preterm infant in the amniocentesis group were excluded because ear infections, hearing loss, and impedance abnormalities are known associations of prematurity (Bluestone & Klein 1988).

* $P = 0{\cdot}06$

distortions of memory and the fact that many children with ear infections may be asymptomatic (Bluestone & Klein 1988). However, in support of the information on ear infections obtained by maternal report, blind audiological assessment showed a trend toward a higher rate of bilateral middle-ear dysfunction. Typically, unilateral impedance problems are more common and males more often are affected (Bluestone & Klein 1988). In our sample, however, children whose mothers had amniocentesis had a higher rate of bilateral abnormalities, and the sexes were affected in equal proportions. Type of medical care, seasonal effects, exposure to ultrasound, and opportunities for infection by exposure to siblings or other children were not associated with ear problems. Exposure to ultrasound, however, needs further investigation with a larger sample, and, because there is marked variability in the amount of exposure to ultrasonic energy during a scan (Miere 1987), precise calibration of machinery and exposure time would be necessary to ensure a valid assessment of the potential effects of ultrasound.

Currently, it is believed that anatomical or physiological abnormality of the eustachian tube is an important, if not the most important, factor predisposing to infection or persistent fluid in the middle ear (Bluestone & Klein 1988). Should the present findings be replicated, it may be hypothesized that reduction of intra-amniotic fluid volume by fluid removal may lead to pressure changes within the ear that may perturb anatomical development. Bilateral impedance abnormality was unrelated to the gestational age when amniocentesis was undertaken or the amount of amniotic fluid withdrawn, although the degree of resolution of these procedure-related variables may be too imprecise or the range too narrow to reveal a relation, should one exist. Moreover, pressure changes may be a function of the proportion of fluid withdrawn which cannot be calculated without data on the total fluid volume at the time of amniocentesis (Finegan 1984). In any case, anatomical development of the ear was not altered sufficiently to disrupt hearing because hearing for speech and pure tones was not significantly affected in our sample.

Early ruptured amniotic membranes may lead to ear infections from infected amniotic fluid (Pestalozza *et al.* 1984). Only one woman in the present study had amniotic fluid leakage following amniocentesis (Finegan *et al.* 1984) and her child had the most marked history of ear problems (i.e. chronic infections leading to myringotomies by 11 months).

Our findings of increased rates of ear problems at 4 years requires replication. As a first step, studies of middle-ear function of children born to women who had amniotic fluid leakage following amniocentesis would provide data in consideration of the hypothesis that fluid loss in the mid-trimester may perturb anatomical development and subsequent middle-ear function. If higher rates of middle-ear problems following amniocentesis are confirmed, they may represent late and subtle effects on the upper respiratory system (cf. Hislop & Fairweather 1982; Report to the Medical Research Council 1978; Tabor *et al.* 1986; Vyas *et al.* 1982). We intend to include a test of lung function when the children are seen in subsequent follow-up.

The study reported here represents the only longitudinal investigation to date of children whose mothers had mid-trimester amniocentesis. The findings may be generalized only to the children of middle and upper social class women who have amniocentesis because of late maternal age. Reassessment of our sample at age 7 years is in progress and will provide information on academic achievement, cognition, and behaviour in the school-age child. We hope that the information arising from our studies may assist in future comparisons of the safety of the various prenatal diagnostic techniques.

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Pretreatment with mifepristone (RU 486) reduces interval between prostaglandin administration and expulsion in second trimester abortion

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Summary. The effect of pretreatment with mifepristone on prostaglandin-induced abortion was investigated in a double-blind randomized trial involving 100 women in the second trimester of pregnancy. The women were randomly allocated to receive either 600 mg oral mifepristone or placebo tablets 36 h before the administration of gemeprost pessaries. The median interval between administration of prostaglandin and abortion was significantly shorter in the mifepristone group (6·8 h) compared with the placebo group (15·8 h). The women pretreated with mifepristone required significantly fewer gemeprost pessaries to induce abortion and experienced significantly less pain than the women who had received placebo.

In 1987, 25% of abortions in England and Wales and 10% of abortions in Scotland were performed in the second trimester of pregnancy (Office of Population Censuses and Surveys 1987; Registrar General for Scotland 1987). Complications of abortion are related to the gestational age and the method used (Cates & Grimes 1981). It is therefore important that procedures for the induction of second trimester abortion minimize long- and short-term morbidity.

Since Karim & Filshie (1970) described the use of prostaglandins for termination of pregnancy, prostaglandins have been widely used to induce abortion. Local instillation techniques have been employed using extra- or intra-amniotic administration of naturally occurring prostaglandins, PGE_2 and $PGF_{2\alpha}$. More recently, prostaglandin analogues have been used in the form of vaginal pessaries to induce abortion. Analogues of the PGE series, gemeprost (16, 16 dimethyl-trans Δ_2-PGE_1 methyl ester) and meteneprost (9 methylene PGE_2) have the advantage of causing fewer gastrointestinal side-effects and less pain as well as having a cumulative abortion rate verging on 100% (Bygdeman *et al.* 1980; Cameron *et al.* 1987). Although the use of prostaglandins has greatly improved procedures for second trimester terminations, induction of abortion at this stage of pregnancy remains a long, distressing and painful experience. Despite improved cumulative abortion rates using prostaglandin analogues, about 20% of women will not have aborted after 24 h of treatment (Cameron & Baird 1984).

Mifepristone (RU 486) is a synthetic steroid which acts as an antigestagen, blocking progesterone receptors in target cells of the endometrium and myometrium. Mifepristone sensitizes the pregnant uterus to exogenous prostaglandin and we have shown previously that by adding a subtherapeutic dose of prostaglandin to treatment with a single dose of the antigestagen, complete abortion can be induced

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Table 1. Characteristics in the two groups

	Mifepristone group ($n = 50$)	Placebo group ($n = 50$)
Age (years)	22·5 (0·6)	21·9 (0·6)
Height (cm)	162 (0·8)	161 (0·9)
Weight (kg)	57·9 (1·1)	60·5 (1·5)
Gestation (weeks)	15·2 (0·2)	15·4 (0·2)
Parous (%)	17 (34%)	14 (28%)

Results are means (SE) values.

in 95% of women in the early first trimester (Rodger & Baird 1987). Preliminary results of a non-randomized study suggested that pretreatment with mifepristone in second trimester terminations significantly reduced the interval between extra-amniotic PGE_2 instillation and expulsion as well as reducing the amount of prostaglandin required (Urquhart & Templeton 1987).

In this double-blind randomized placebo-controlled trial we have investigated whether pretreatment with a single 600-mg dose of mifepristone reduces the interval between administration of gemeprost pessaries and expulsion in women seeking termination of pregnancy between 12 and 18 weeks gestation.

Subjects and methods

A total of 100 women with uncomplicated pregnancies of between 12 and 18 weeks gestation was recruited to this study. All women were 16 years or older and had no serious medical disorders and were recruited after admission to the Simpson Memorial Maternity Pavilion. Before admission, all the women had been counselled by two doctors and found to have grounds for termination of pregnancy under the provision of the 1967 Abortion Act. Local ethics committee approval was granted for the study, and written informed consent was obtained from each woman before treatment, with parental or guardian consent where necessary.

Pregnancy was confirmed by measurement of urinary hCG, and gestational age was assessed by clinical examination and pelvic ultrasonography. Blood was taken to estimate haemoglobin before treatment.

After recruitment the women were allocated by random number table to receive three oral tablets of either 3×200 mg mifepristone ($n = 50$) or placebo ($n = 50$). No dietary restrictions were imposed and observation of temperature, blood pressure and pulse rate were made hourly for 4 h. During these 4 h an accurate record of any side-effects or symptoms was made.

After an interval of 36 h, the women were questioned closely about any symptoms, in particular about vaginal bleeding or pelvic pain, before the administration of gemeprost (Cervagem, May & Baker Ltd). A 1-mg gemeprost vaginal pessary was inserted into the posterior fornix and this treatment was repeated every 3 h until either abortion had occurred or a maximum of five pessaries had been given. If abortion had not occurred with 24 h of the first pessary a further course of up to five pessaries was given. Those women who had still not aborted 48 h after the insertion of the first pessary received an intravenous infusion of oxytocin supplemented, if necessary, by further gemeprost pessaries.

All women remained in bed throughout treatment with gemeprost. An intravenous infusion was sited before the insertion of the pessary and although oral fluids were allowed, solid foods were withheld. Temperature, blood pressure and pulse rate were measured every 3 h and any symptoms experienced were recorded. Prophylactic medication was not prescribed, but analgesia and anti-emetics were given as required: 7·5 mg of intramuscular diamorphine for pain and 50 mg of intramuscular cyclizine for vomiting. Intramuscular syntometrine (ergometrine maleate, 500 μg, and oxytocin, 5 iu, Sandoz

Table 2. Symptoms experienced after mifepristone or placebo administration

Symptom	Mifepristone group ($n = 50$) n (%)	Placebo group ($n = 50$) n (%)
Bleeding	3 (6)	0 (0)
Pain	17 (34)	10 (20)
Headache	17 (34)	8 (16)
Tiredness	13 (26)	10 (20)
Anorexia	10 (20)	3 (6)
Hot flushes	4 (8)	2 (4)
Nausea	14 (28)*	4 (8)
Vomiting	10 (20)**	2 (4)**
Diarrhoea	0 (0)	3 (6)
Dysuria	2 (4)	1 (2)
Faintness	1 (2)	1 (2)
Indigestion	1 (2)	1 (2)

* $P<0·02$, $\chi^2 = 5·488$, d.f = 1

** $P<0·05$, $\chi_2 = 4·640$, d.f = 1

Table 3. Prostaglandin induction-to-abortion interval

	Mifepristone group ($n = 49$)	Placebo group ($n = 50$)
Induction-to-abortion interval (h)	6·8 (2·0–67·8)*	15·8 (5·9–95·6)*
Number of pessaries used	3 (1–10)**	5 (2–10)**
Injections of analgesia per woman	1·1 (0·1)†	1·5 (0·2)†

The data presented show median (range) except for analgesia which is presented as mean (SE).
* $P<0{\cdot}0001$, $U = 339$
** $P<0{\cdot}0001$, $U = 370$.
† $P<0{\cdot}05$, $U = 975$.

Products Ltd) was injected at expulsion. Unless the products of conception were deemed complete, surgical evacuation of the uterus was performed under general anaesthesia.

The women were allowed home after appropriate contraceptive counselling and were reviewed 4–6 weeks later. At the follow-up visit the women were asked about vaginal bleeding and any symptoms subsequent to the abortion. A vaginal examination was performed and a venous blood sample was taken for haemoglobin estimation. The women were discharged from our care after this visit if there were no problems.

Statistical analysis

The Mann–Whitney *U*-test and χ^2-test have been used. The data are expressed as mean (SE) or median (range) values.

Results

There were no statistically significant differences in the characteristics of the women between the two groups (Table 1).

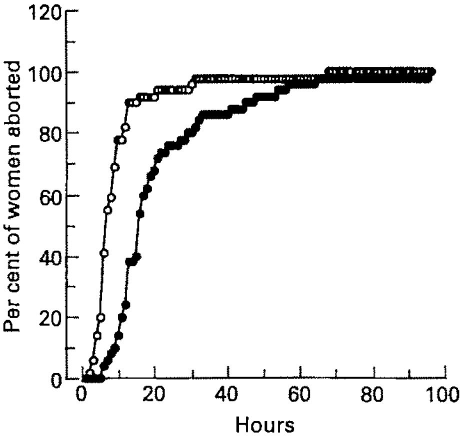

Fig. 1. Cumulative abortion rate. ○, RU 486, $n = 49$; ●, placebo, $n = 50$.

One woman who received her first gemeprost pessary 51 h after taking 600 mg of mifepristone has been excluded from the analysis of treatment outcome following prostaglandin because abortion was already well advanced.

Three women in the mifepristone group reported minimal spotting of blood from the vagina in the 36 h before prostaglandin treatment. Pelvic pain was a commonly reported symptom in both groups, with 17 (34%) women in the mifepristone group and 10 (20%) in the placebo group experiencing mild dysmenorrhoeic-like discomfort. Headaches were also common in both groups as was a feeling of tiredness, but significantly more women in the mifepristone group experienced both vomiting and nausea during this 36-h period than women in the placebo group (Table 2).

Pretreatment with mifepristone significantly decreased the interval between administration and abortion. The median (range) time interval to abortion after the insertion of the first gemeprost pessary was only 6·8 (2·0–67·8) h in the mifepristone group compared with 15·8 (5·9–95·6) h in the placebo group ($P<0{\cdot}0001$) Women who received the antigestagen required

Table 4. Frequency of incomplete abortion in the two groups

	Mifepristone group ($n = 49$) n (%)	Placebo group ($n = 50$) n (%)
Retained placenta	26 (53)	36 (72)
Incomplete abortion	15 (31)	10 (20)
Complete abortion	8 (16)	4 (8)
Surgical evacuation of uterus	45 (92)	48 (96)

significantly fewer gemeprost pessaries to induce abortion (median 3, range 1–10) than the women who received the placebo (median 5, range 2–10) ($P<0.001$). The requirement for analgesia was also significantly less in the mifepristone group. Following mifepristone in this group the mean number of injections of 7·5 mg diamorphine required per woman was 1·1 (SE 0·1) compared with 1·5 (SE 0·2) injections per woman in the placebo group (Table 3).

Of the 49 women available for analysis in the mifepristone group 46 (94%) aborted during or following the first course of pessaries (that is during the first 24 h of prostaglandin treatment), 2 (4%) women aborted after seven pessaries, and only one woman required supplementary oxytocin following two courses of pessaries to induce abortion. In the placebo group 40 (80%) aborted during the first 24 h of treatment, 4 (8%) required supplementary oxytocin, and 2 (4%) needed further prostaglandin in addition to oxytocin to induce abortion (Fig. 1).

There were no reported serious adverse reactions to gemeprost during treatment in either group. Only one woman (in the placebo group) required blood transfusion; she was given a 2-unit transfusion of red cell concentrate following an episode of heavy vaginal bleeding which occurred during surgical evacuation of the uterus.

The frequency of vomiting during prostaglandin treatment was similar in both groups, 20 (41%) women in the mifepristone group and 20 (40%) in the placebo group vomited. Although fewer women in the mifepristone group experienced diarrhoea (5 compared with 10 in the placebo group) this difference was not statistically significant.

There was a high rate of retained placenta and incomplete abortion in both groups and most women had surgical evacuation of the uterus, reflecting existing hospital practice (Table 4).

Overall, 43 (86%) women in the mifepristone group and 41 (82%) women in the placebo group returned for review. The median duration of bleeding following abortion was 12 (range 3–41) days in the mifepristone group and 14 (range 0–25) days in the placebo group. Five women in the mifepristone group and six in the placebo group were treated with antibiotics in the weeks between abortion and review because various pathogenic organisms were isolated from their endocervical swabs. Only one woman (in the mifepristone group) required hospital admission because of pelvic infection subsequent to retained products of conception. *Chlamydia trachomatis* was isolated from her swabs.

In both groups the concentration of haemoglobin had increased significantly following abortion.

Discussion

This double-blind randomized placebo-controlled trial of mifepristone or placebo treatment before prostaglandin-induced abortion has confirmed the preliminary findings by Urquhart & Templeton (1987). Pretreatment with mifepristone reduced the interval between prostaglandin administration and expulsion significantly and reduced the amount of prostaglandin required, leading to a much reduced need for opiate analgesia. There is evidence to suggest that mifepristone sensitizes the uterus to the oxytocic action of prostaglandins by releasing endogenous prostaglandins from the decidua (Bygdeman & Swahn 1985, Smith & Kelly 1987), and certainly this would explain both the reduced induction-to-abortion interval and small requirement for prostaglandin after priming with mifepristone.

Bydgeman & Christensen (1983) reported a shortening of the prostaglandin induction-to-abortion interval after a 12-h pretreatment with laminaria tent. The mean duration of labour in the second trimester induced by 16-phenoxy-PGE_2 (sulprostone) or 15-methyl-$PGF_{2\alpha}$ was shortened to around 10 h after priming with laminaria, and over 90% of women aborted within 24 h of prostaglandin administration. However, the amount of prostaglandin required to induce abortion was higher than that required with mifepristone in our study, and subsequently the frequency of prostaglandin-related side-effects was also higher. Another obvious though practical consideration is the route of administration of the priming agent—much more skill is needed to insert the laminaria tent than to give mifepristone.

This combination of mifepristone pretreatment with vaginally administered gemeprost pessaries provides a simple, non-invasive and highly effective method of second trimester termination. Labour is dramatically shortened following the antigestagen, less prostaglandin is required and fewer women experience severe pain; this treatment regimen represents a vast improvement in terms of safety and acceptability.

Both mifepristone and prostaglandin analogues will induce softening and dilatation of the cervix in women at 7–11 weeks gestation (Radestad *et al.* 1988). This softening which is associated with a change in the collagen and ground substance of the cervix, occurs physiologically in late pregnancy before the onset of labour. The length of labour and the occurrence of spontaneous delivery is directly related to the degree of cervical softening and dilatation before labour (Uldbjerg *et al.* 1983). Our findings suggest that priming of the uterus and cervix with mifepristone would have wide application in spontaneous and induced labour if it can be shown to be without hazard to the fetus.

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Using Lamicel to expose high cervical lesions during colposcopic examinations

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Summary. Women with abnormal cervical cytology and an unsatisfactory colposcopic examination were offered Lamicel in an attempt to expose the entire transformation zone. The sponge, which softens, dilates and effaces the cervix, was passed intracervically in 41 patients in whom the entire squamocolumnar junction could not be seen. After 3–4 h the sponge was removed and colposcopy repeated. In 29 of the 41 patients the lesion and the squamocolumnar junction were now fully visible. Twenty-five of these patients were spared a cone biopsy.

The advent of colposcopy allowed premalignant ectocervical lesions to be diagnosed confidently and ablated safely by local treatment. This advance made a dramatic impact on the number of diagnostic cone biopsies performed. However, if there are atypical cells on a cytological smear and if the squamocolumnar junction is not seen in its entirety, then to exclude an early invasive cancer in the area beyond the view of the colposcope, a cone biopsy is mandatory (Singer 1983). This situation occurs in 1 in 4 patients over the age of 40, 1 in 6 between the ages of 30 and 40, and 1 in 40 in those below 30 years of age (Shingleton & Orr 1987). Compared with local destructive therapy, the major disadvantages of a cone biopsy are surgical morbidity and the impact on future reproductive potential. The risk of a late miscarriage increases 10-fold in women who have had a cone biopsy and they are also at a risk of preterm labour, chorioamnionitis, cervical dystocia, caesarean section (Myllynen & Karjalainen 1984; Larsson *et al.* 1983; Mionian & Andersch 1982) and possibly subfertility. Even in those with no desire for further children a cone biopsy presents a significant risk of surgical morbidity from haemorrhage (4–21%) (Rubio *et al.* 1975; Jones & Buller 1980; Larsson *et al.* 1983, Luesley *et al.* 1985) and stenosis (Byrne 1966, Byrne *et al.* 1987; Hollyhock & Chanen 1972; Larsson 1983).

Lamicel (Cabot Medical, Langhorne, PA, USA) is a soft, dried and compressed polyvinyl alcohol sponge impregnated with magnesium sulphate (Johnson 1988*a*, 1989*a*, 1989*b*). When placed in the cervical canal it becomes moist and expands, inducing cervical softening, effacement and dilatation (Johnson *et al.* 1985, Johnson & Moodley 1988) The only reported complication associated with Lamicel is dumbbelling and subsequent hydrometria (Johnson 1988*b*). In this study we tested the hypothesis that cervical configuration could be changed by Lamicel so that full inspection of the transformation zone would become possible.

Before offering Lamicel to patients in an attempt to expose lesions beyond the view of the colposcope, two pilot studies were performed to ensure that the sponge would not alter the colposcopic or histological appearances of abnormal lesions.

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Subjects and methods

Histological pilot study

Forty-seven women with abnormal cervical cytology (cytological pattern suggesting dysplasia) and a colposcopic lesion involving the canal, were divided into two groups (according to the month of presentation). Lamicel was passed into the cervical canal of the intervention group and it remained *in situ* for 3–4 h. After removing the sponge a colposcopically directed punch biopsy was taken from the suspicious lesion. The women in the control group did not have Lamicel inserted but they were examined colposcopically and had a punch biopsy taken. The biopsies were stained with haematoxylin and eosin and examined histologically by one pathologist who was blind to the group allocation. Sections were graded for degree of cervical intraepithelial neoplasia (CIN), stromal oedema, inflammatory changes, tissue compression, general structure and the degree of surface disruption, which was graded from 0 (no surface disruption) to 3 (only the basal layer remaining).

Colpophotography and colposcopic topographic pilot study

Six patients undergoing cone biopsy or hysterectomy for CIN were exposed to a pre-operative transcervical Lamicel for 4–6 h after an initial colposcopic and colpophotographic examination. The postoperative cervical specimen was then opened and immediately examined *in vitro* under the colposcope. The topographical features of the cervix before and after Lamicel exposure were compared.

Clinical study

Fifty-eight women, all with abnormal cervical cytology and unsatisfactory colposcopic examinations on two occasions, were offered Lamicel. The patients were selected from four colposcopy clinics in Leeds over an 11-month period. As far as possible, all of the women who presented with an unsatisfactory colposcopy during the 11-month period are included but some women who presented to one clinic may not have been recruited because they were treated with a laser cone biopsy or laser excision at their first visit.

An unsatisfactory colposcopy was defined as a primary colposcopic examination where the entire transformation zone could not be inspected despite manipulating a bivalve (Cusco's) vaginal speculum and using Dejardin's or Kogan's endocervical forceps. A tenaculum was also applied to a cervical lip if it was thought that this could help avoid an unsatisfactory colposcopy. If the lesion remained beyond the view of the colposcope, then the patient was offered Lamicel. Twelve patients were excluded: five because they preferred a one-stage procedure (cone biopsy or hysterectomy), in six the cervix was too stenotic to accept a 3-mm-diameter sponge, and one woman had colposcopic stigmata of microinvasive disease. The remaining women returned on a separate occasion and were colposcoped again. If the entire lesion still remained out of view, then a 3-mm-diameter Lamicel was passed into the cervical canal up to its distal collar. A tenaculum was invariably required to stabilize the cervix. The women were examined again 3–4 h later and the sponge was removed. With each patient acting as her own control, the procedure was declared a success only if the entire lesion and transformation zone could be confidently seen and a positive colposcopic diagnosis made. A biopsy was taken and the event was recorded colpophotographically. It was considered a failure if the lesion remained out of view or if the surface was seen at such an acute tangent that a colposcopic diagnosis could not be made with confidence.

Results

Histological pilot study

The frequency and grade of CIN were similar in the study and control groups In five biopsies from each group at least 50% of the epithelium was columnar (i.e. the biopsy was predominantly endocervical). Disruption of the layers of the squamous epithelium appeared more severe in those women in whom Lamicel had been used (Table 1) ($P<0{\cdot}02$ according to Fisher's test). However, there were only two specimens where this was so severe as to prevent grading of the CIN lesion, and in all biopsies the presence of stromal invasion could be confidentally excluded. Exposure to Lamicel for 4 h did not produce any alteration in cellular architecture, stromal oedema or tissue compression.

Colpophotography and colposcopic topographic pilot study

The insertion of Lamicel did not make any

Table 1. The effect of Lamicel on the histological features of a cervical biopsy

	Cervix exposed to Lamicel ($n = 26$)	Control group ($n = 21$)
Number of specimens with no or mild surface disruption (grade 0–1)	15 (58%)	19 (90%)
Number of specimens with moderate to severe surface disruption * (grade 2–3)	11 (42%)*	2 (10%)
Number of cases with stromal oedema	5/20 (25%)	6/16 (37%)

* Including the specimen illustrated in Fig. 2 and one other with surface disruption severe enough to prevent adequate grading of the CIN However, microinvasive disease could be excluded

difference to the topographical appearances of mosaicism and punctation.

Clinical study

Five of the 46 women who were recruited had a second colposcopic examination which was subsequently found to be satisfactory and a confident colposcopic diagnosis could be made. Of the remaining 41, the entire transformation zone was visible in 29 patients (see Fig. 1); 21 of them were treated by local ablation of the transformation zone, four were treated with a therapeutic cone biopsy, and four were followed up In 12 women Lamicel failed to expose the squamocolumnar junction adequately (Tables 2 & 3). The best results were obtained in the younger women (χ^2-test for trend = 7·15; P<0·02) and in those who had not had previous surgery (χ^2-test for trend = 9·23; P<0·002).

Of the 41 women treated with Lamicel 28 experienced discomfort as the sponge was passed, and 10 complained of period-like cramps which lasted for up to 20 min after insertion. There was no evidence of any infection after Lamicel.

Discussion

A cone biopsy has a considerable morbidity and a slight mortality. Consequently several techniques have been proposed to try and convert an unsatisfactory colposcopy into one which is satisfactory. Prescribing oral oestrogen (100 μg for 5 days) may soften the cervix and improve colposcopic inspection (Cartier 1984; Prendiville *et al.* 1986). Microcolposcopy and microhysterocolposcopy (Hamou & Taylor 1982) and making a radial incision in a cervix with a laser to open the canal may expose high lesions but these techniques are unpleasant for the patient and require additional expertise. On occasions an unsatisfactory colposcopy can become satisfactory by persistent manipulation with the vaginal speculum or endocervical forceps, and inspection of the endocervix may also be possible at a repeat examination if it is performed at a different stage of the menstrual cycle The cervical os is softer and the diameter of the canal is at its greatest before ovulation and during menstruation (Johnstone *et al.* 1974). Five of our subjects were spared a cone biopsy simply by repeating the examination.

Using Lamicel to enable a satisfactory colposcopic examination of the cervical canal was a particularly effective technique in young nulliparous women who tend to have a small cervical os, but the squamocolumnular junction is not high up the canal. The squamocolumnular junction in older and menopausal patients tends to be high up the canal and is difficult to see even if the cervix is dilated. Those women who have had a previous surgical cone biopsy also respond badly to Lamicel; in 50% it is impossible to pass the sponge as the cervix is so stenotic and fibrotic and moreover the squamocolumnar junction is so high up the canal that the lesions still remain out of view despite medical dilatation. Fortunately it is the younger nulliparous women with their full reproductive potential before them who have most to gain by avoiding a surgical cone biopsy.

Lamicel is a dried sponge which expands. It does not appear to affect the histological appearances of the normal or pathological cervix. The histological features of the normal cervix which has been exposed to Lamicel have been reported and no gross change that would be likely to confuse the histopathologist can be detected (Nicolaides *et al.* 1983; Norstrom *et al.* 1988). Hale & Pion (1972) investigated the use of laminaria and reported similar results. In our pilot study the

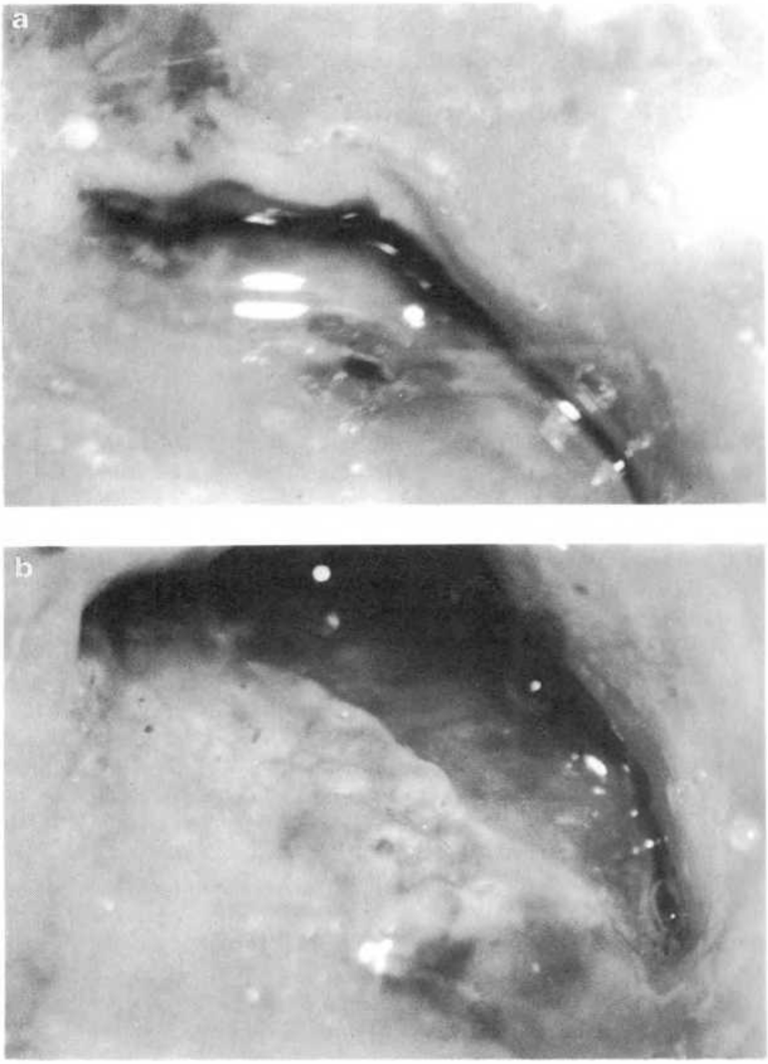

Fig. 1. Colpophotograph before (a) and after (b) Lamicel (note the relative position of the dysplastic lesion before and after Lamicel).

histological features of the pathological cervix which had been exposed to Lamicel were indistinguishable from those in a control group not exposed to Lamicel. However, Lamicel can traumatize the surface epithelium and although this is not severe enough to affect the colposcopic appearance it can affect the histological grading of a CIN lesion. This surface disruption is limited to small areas and will not affect the patient's management but it is a limitation of the techniques. The most severe example is shown in Fig. 2.

It was initially considered that the expanding sponge might alter the topographical appearances of the delicate cervical epithelium. Before embarking on clinical work it was necessary to confirm that the sponge did not affect the colposcopic appearances in hysterectomy specimens. Warty atypia, CIN and squamous metaplasia were found to retain their colposcopic appearances, despite exposure of Lamicel. The postoperative specimens could be opened longitudinally and confirm that Lamicel does not alter the topography of either the ecto- or endocervix. This has also been our clinical experience. This is not surprising because when Lamicel is moist it is extremely soft and it exerts a radial pressure of only 14kPa compared with 190kPa exerted by laminaria digitata (Wheeler & Schneider 1983). Furthermore, Stubblefield

Table 2. Characteristics of 58 consecutive women with an 'unsatisfactory colposcopy' (squamocolumnar junction not seen)

	Total number recruited	Number offered Lamicel	Success for Lamicel *n* (%)
Age (years)			
<30	19	15	13 (87)
30–40	19	14	11 (79)
>40	20	12	5 (42)
Previous cervical surgery	25	16	7 (44)
Nulliparous	12	11	9 (82)
Total	58	41	29 (71)

(1980) showed that cervical dilatation in pregnancy was not soley a function of the force exerted because the dilatation achieved was actually greater than the diameter of the expanding tent.

The improved colposcopic view that Lamicel induces may be explained by biochemical studies. The change in amount of visible ectocervix is related to the cervical dilatation and effacement which depends on its microstructure and chemistry. The 'elderly cervix' is more fibrous with a greater collagen content and a reduced collagenase activity (Roberts & Denholm 1988). Lamicel decreases collagen content and increases collagenase activity (Robinson & Filshie 1989; Norstrom *et al.* 1988). Although the precise mode of action is unknown, it probably involves both biochemical and mechanical mechanisms.

The theoretical advantage of Lamicel over laminaria and Dilapan is that it is a soft sponge and it exerts only a fraction of the radial pressures exerted by these alternative tents (Wheeler & Schneider 1983). Dilapan, although more efficient as a dilator, exerts considerable radial forces and tends to be gripped by the cervix. Moreover, it shrinks in length as its diameter increases and this theoretically imparts shearing stress to the cervical epithelium thus limiting its use as an adjunct to colposcopy. Although Lamicel was associated with surface disruption of the endocervical epithelium, it is likely that this is due to the difficulty in obtaining a 'clean' punch biopsy from the canal rather than due to epithelial changes. Generally, it was only possible to obtain a biopsy from the canal if the cervix had been exposed to Lamicel, whilst in the control group it was often only possible to biopsy the ectocervix.

Lamicel can reduce the need for a cone biopsy in patients who present with an 'unsatisfactory colposcopy'. This simple, safe technique is a well-tolerated, effective diagnostic procedure (95% CI of the success rate is 57–85%) with obvious advantages, particularly with the

Table 3. Outcome in 58 women with an unsatisfactory colposcopy

Outcome/management	Number of patients
Lamicel not used (*n* = 17)	
Opted for cone biopsy/hysterectomy	5
Lamicel could not be passed	6
Repeat colposcopy satisfactory	5
Ectocervical suspicion of microinvasion (confirmed histologically)	1
Lamicel used (*n* = 41)	
Lamicel failed, treated by cone biopsy	12
Lamicel succeeded (*n* = 29)	
Laser ablation	8
Electrodiathermy	13
Metaplasia only (managed by follow-up)	4
High lesion (treated by cone biopsy)	3
No lesion seen (treated by cone biopsy)	1

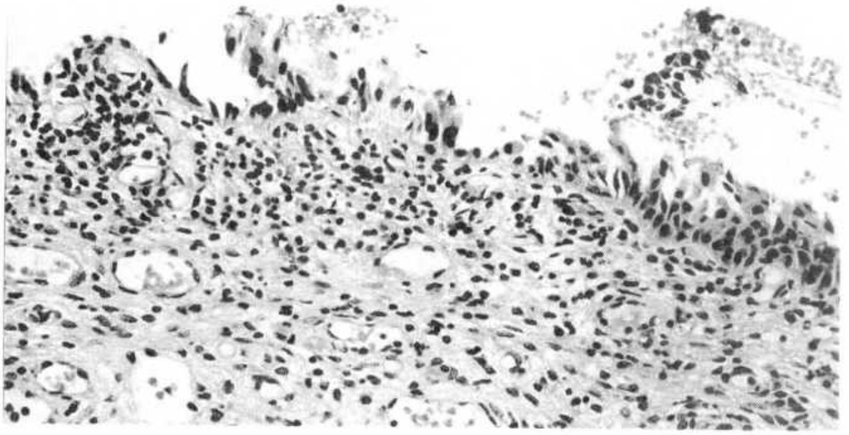

Fig. 2. The most severe example of epithelial surface disruption caused by Lamicel.

increasing prevalance of older nulliparous patients with abnormal cervical smears who still want a family.

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Diagnosis of deep venous thrombosis in pregnancy: a new role for diagnostic ultrasound

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Summary. Ultrasound has recently become accepted as an accurate imaging technique in the diagnosis of deep vein thrombosis. Real-time and duplex ultrasound findings in six pregnant women with clinically suspected deep venous thrombosis are described.

Deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE) remain major sources of maternal mortality and morbidity. Around half of these deaths occur antenatally (Report on Confidential Enquiries into Maternal Deaths in England and Wales 1979–81). The diagnosis of DVT is critical as its presence places the woman at substantial risk of PTE, while anticoagulation without a firm diagnosis may subject the woman to unnecessary and potentially dangerous anticoagulant therapy (Greer 1989). However, the clinical diagnosis of DVT is notoriously unreliable. Fewer than 50% of DVTs involving major proximal veins in non-pregnant subjects are recognisable clinically, while venography substantiates the diagnosis in only about 40% of subjects with clinical findings compatible with DVT (Genton & Turpie 1980; Ramsey 1983). Objective assessment is therefore required. Venography has been the 'gold standard' of diagnosis, but it is invasive and exposes the patient to X-rays and contrast material. These features often make obstetricians reluctant to use venography in pregnant women unless there is a high degree of clinical suspicion. Non-invasive techniques such as impedance plethysmography have been used in pregnancy (Clarke-Pearson & Jelovsek 1981; Greer 1989) but these lack the sensitivity and specificity which are required for reliable diagnosis and guidance for subsequent treatment.

Recently real-time ultrasound scanning has been used successfully in the diagnosis of DVT in the non-pregnant. It has the advantage of being non-invasive, quick, and uses standard scanning equipment which is available in most obstetric units. We have used this method in six patients to confirm or negate a clinical diagnosis of DVT, in each case the scan provided diagnostic information allowing treatment to be instituted, withheld or altered. These patients and the methods used to study the veins are now described.

Subjects and methods

During a 2-year period six patients at various stages of pregnancy were referred for ultrasound assessment of clinically suspected DVT. The veins were examined with a 5-MHz electronically focused linear array transducer (Acuson, DSL). Four of these patients were also examined by duplex Doppler (Acuson) The femoral veins were assessed in the supine position; the popliteal and upper tibial veins were examined in the lateral decubitus position with the knees flexed to 30°. All veins were imaged in the longitudinal and transverse planes. The lumen was inspected for the presence or absence of visible flow and thrombus. Compressibility was assessed by applying gentle pressure with the transducer. A vein was considered normal if the lumen was obliterated by gentle pressure on transverse scanning. In some subjects the change in calibre during the Valsalva manoeuvre was

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assessed. In four cases duplex Doppler examination of the femoral and popliteal veins was undertaken at the same examination. The presence of respiratory variation in flow in the upper femoral vein was taken as indirect evidence of patency of the iliac veins. Augmentation, that is an increase in flow on gentle squeezing of the calf or dorsiflexion of the foot was taken as indirect evidence that the distal veins were patent. In each case the examination took approximately 15–20 min. In one patient there was strong suspicion following the ultrasound examination to suggest the presence of illiac thrombus. This patient had bilateral ascending venography with non-ionic contrast medium which confirmed the ultrasound findings. Three patients had follow-up ultrasound scans due to increasing leg discomfort or to monitor improvement after institution of therapy.

Patient no. 1

A 29-year-old primigravida presented at 38 weeks gestation with a painful left leg which was cyanosed, swollen, warm and tender. Real-time ultrasound examination suggested the presence of proximal thrombus in the deep veins in the inguinal region with sluggish flow in the femoral vein on Duplex scanning. Ascending venography was used to delineate the extent of the thrombus. A filling defect consistent with thrombus in the distal part of the external iliac vein was found. The patient was fully anticoagulated with intravenous heparin for 7 days, then started on chronic heparin therapy (10 000 iu subcutaneously twice daily). The initial symptoms and signs had resolved before chronic heparin therapy was begun. Seven days later she complained of further leg pain. Clinical examination revealed no positive findings. Further real-time ultrasound showed extension of the thrombus into the femoral vein to mid-thigh and the long saphenous vein. The patient was again started on full anticoagulation with heparin before delivery.

Patient no. 2

A 31-year-old para 0 + 1 was admitted at 35 weeks gestation with severe pain in the left thigh and difficulty in walking. On examination she had left calf tenderness and rubor. Real-time ultrasound examination showed thrombus in the femoral vein extending from pelvis to mid-thigh and in the veins of the left calf. She was anticoagulated. One week later, despite clinical improvement in the leg, ultrasound showed little change in the extent of the thrombus, and intravenous heparin was continued for a further period. Further scanning demonstrated resolution of the thrombus and recanalization before induction of labour at 40 weeks gestation and continued improvement postnatally while on oral anticoagulant therapy.

Patient no. 3

A 33-year-old primigravida was admitted at 30 weeks gestation with left groin pain, swelling of the left leg and marked tenderness over the left femoral vein just below the inguinal ligament. Ultrasound examination showed extensive thrombus in the left superficial femoral vein, extending from mid-thigh to pelvis, and she was anticoagulated Subsequent ultrasound examination showed considerable improvement in the thrombus with shrinkage and recanalization. Delivery was uncomplicated and ultrasound scans showed continued improvement with anticoagulant therapy in the puerperium.

Patient no. 4

A 31-year-old para 3 + 0 was admitted at 21 weeks gestation with a grossly swollen and painful left leg, which was dusky and warm. Real time ultrasound showed extensive thrombus in the left femoral and popiteal veins. She was fully anticoagulated with intravenous heparin for 7 days then started on chronic heparin therapy. The pregnancy progressed without further complication.

Patient no. 5

A 28-year-old para 1 + 0 presented at 37 weeks gestation with a painful swollen left leg. At the time of presentation she gave a history of a spontaneous deep venous thrombosis (DVT) at the age of 17 years which she had not previously admitted. On examination the left leg appeared swollen but otherwise there were no positive clinical findings. Duplex ultrasound scanning showed no evidence of thrombus. No treatment was instituted and the pregnancy remained uncomplicated.

Patient no. 6

A 34-year-old insulin-dependent diabetic, para 2

+ 1, weighing 136 kg booked at 7 weeks gestation. She gave a history of two previous DVTs. One occurred spontaneously and one after an appendicectomy. The latter DVT was followed by two pulmonary thrombo-emboli. None of these thrombotic events was associated with pregnancy. A thrombotic screen showed no obvious abnormality. In view of her high-risk status she received prophylactic subcutaneous heparin, 10 000 iu twice daily, from the second trimester. At 32 weeks gestation she complained of a painful swollen left leg. Clinical examination showed no gross changes although assessment was difficult due to her obesity. Real-time ultrasound identified the femoral veins throughout their length and no thrombus was evident. The pregnancy remained essentially uncomplicated.

Discussion

There are now several descriptions of the use of this technique in the diagnosis of DVT (Lensing *et al.* 1989; Aitken & Godden 1987). A recent study comparing venography with real-time ultrasound has shown that the latter technique has a sensitivity of 94% and a specificity of 100% (Aitken & Godden 1987), results confirmed by other workers (Sullivan *et al.* 1984; Cronan *et al.* 1987; Lensing *et al.* 1989). With this technique the veins and thrombi can be seen directly (Sullivan *et al.* 1984; Aitken & Godden 1987; Lensing *et al.* 1989). The normal femoral and popliteal veins appear free of soft tissue echoes (Fig. 1) and are easily compressed during an ultrasound examination. When thrombus is present a relatively echogenic soft tissue mass is seen within the vein (Figs 2 & 3) which will prevent the vein collapsing on compression. Compressibility appears to be a powerful diagnostic criterion (Lensing *et al.* 1989). The normal response of an increase in diameter of the vein in association with the Valsalva manoeuvre is also diminished or absent with venous occlusion by thrombus (Effeney *et al.* 1984). Acute and chronic thrombi may also be distinguished on scanning as the latter are usually highly echogenic (Coelho *et al.* 1982). The disadvantages of this technique are that the distal segments of the calf veins cannot be inspected directly and neither can the iliac veins (Cronan *et al.* 1987). The popliteal-femoral segment within the adductor hiatus may also be difficult to see (Aitken & Godden 1987). The addition of Doppler assessment of the veins may give further indirect information indicating the patency of the iliac veins. Normal respiratory fluctuation in flow in the femoral veins excludes complete thrombosis of the illiac vein (Zweibel 1988). The patency of tibial veins may be ascertained indirectly by demonstrating augmentation of flow on gently squeezing the calf (Zweibel 1988). Loss of augmentation indicates thrombosis between the transducer and region of the calf squeezed.

In the six patients described in this paper, we found that the loss of normal compressibility was the most specific and reproducible finding indicating the presence or absence of DVT. This is in keeping with the results in the non-pregnant state (Aitken & Godden 1987; Lensing *et al.* 1989). Inspection of thrombus within the lumen was technically more difficult and depends on the quality of the ultrasound equipment employed and the operator's skill. In all four subjects with positive results we demonstrated the presence of echogenic thrombus within the lumen of the vein. We suspect, however, that very fresh thrombus which can be of low echogenicity may be more difficult to see and echogenicity can also be mimicked by turbulent flow within the vein (Lensing *et al.* 1989). In the four patients with positive examinations, the diagnosis of DVT was made on the basis of the real-time ultrasound findings. Each of these four patients was also assessed by duplex Doppler. The Doppler examinations in all four demonstrated loss of respiratory fluctuation in flow in the involved upper femoral vein. In three patients we demonstrated loss of augmentation of flow indicating distal thrombus. In view of this we would suggest that real-time assessment of compressibility of the vein was the most valuable indication of the presence or absence of thrombus; the addition of Doppler examination gave more information on the extent of the thrombus but did not play a major role in the diagnosis of thrombus or in the management of the patient.

This paper illustrates that this technique can be successfully employed to diagnose DVT in the pregnant woman. In view of the ease and safety of this technique it can also be used repeatedly to monitor resolution of the thrombus as used in several of our patients. A further advantage of this technique is its ability to diagnose other problems such as a Baker's cyst which might mimic DVT. The technique is non-invasive and uses ultrasound equipment which is available in most obstetric units. It can therefore be used if there is any suspicion of possible DVT

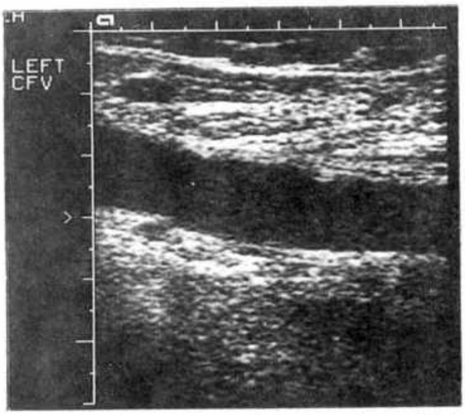

Fig. 1. Longitudinal scan of a normal femoral vein.

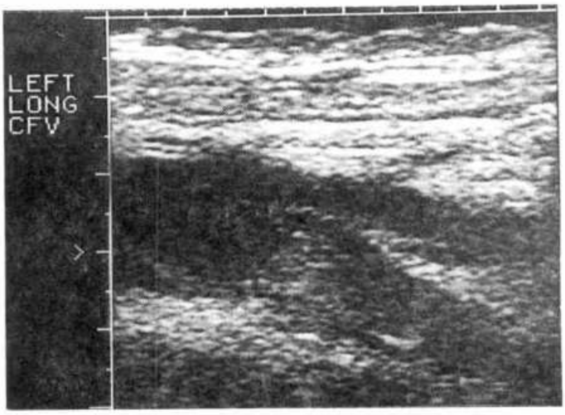

Fig. 2. Longitudinal scan of femoral vein containing echogenic thrombus.

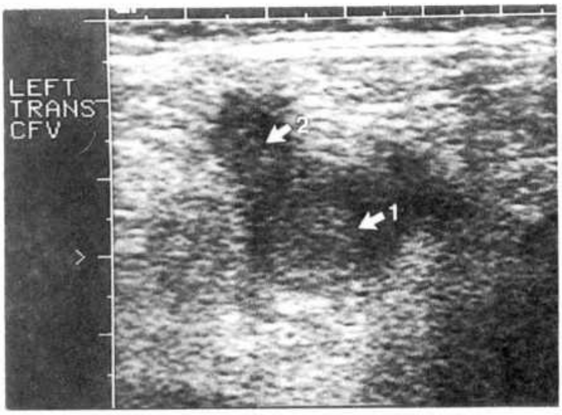

Fig. 3. Transverse scan of a femoral vein containing echogenic thrombus (arrow 1). There is also thrombus in the long saphenous vein (arrow 2).

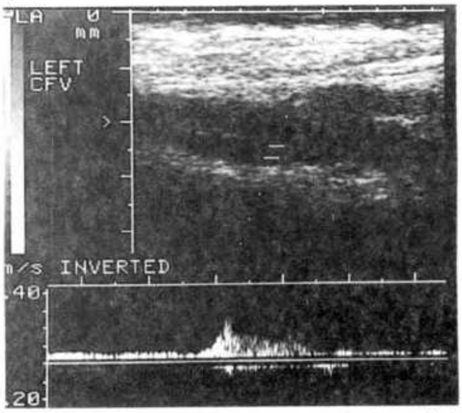

Fig. 4. Duplex scan of a femoral vein in which recanalization has occurred. Doppler demonstrates augmentation of flow in the patent portion on gently squeezing the calf. Recanalized portion indicated by horizontal lines.

where previously the potential hazards of venography may have deterred the use of this technique for cases with equivocal symptoms and signs. In view of the poor correlation between clinical findings and objective diagnosis, a non-invasive technique such as real-time ultrasound may be of great value in obstetric practice. Venography is not made redundant by this technique as it may be required to demonstrate pelvic veins inaccessible to ultrasound, or confirm an occasionally equivocal result as illustrated in our first patient. However, firm diagnosis of DVT on ultrasound can allow anticoagulation to be given without recourse to venography and so substantially reduce the number of venograms performed in pregnancy. It would be difficult to perform a sizeable study of ultrasound versus venography in antenatal patients, and the ethics of such a study would be questionable in view of the proven efficacy of ultrasound diagnosis in the non-pregnant. We would suggest that, as in our unit, real-time ultrasound be employed as the investigation of choice for primary diagnosis of DVT in antenatal patients with venography being reserved for further investigation of equivocal ultrasound examinations.

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How frequently need vaginal smears be taken after hysterectomy for cervical intraepithelial neoplasia?

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Summary. A retrospective longitudinal review identified 341 women who had had a hysterectomy in association with CIN 3, in Tayside Region, during the years 1967–1977; 219 (64%) had completed 10 years of cytology follow-up and of 140 women eligible for 15-year smears 79 (56%) completed the 15-year follow-up. Eight (4%) of the 219 patients developed abnormal cytology, but in six, smears reverted to normal spontaneously. Two patients had persistently abnormal smears and vaginal intraepithelial neoplasia (VAIN) was diagnosed. Only one patient completing 15-year follow-up had an abnormal smear and VAIN later diagnosed. No patient over this 15-year period developed invasive vaginal carcinoma. Sixty vaginal carcinomas were identified during the period 1957–1987 from the gynaecology cancer register; only one was associated with a previous diagnosis of CIN 3 at hysterectomy. With such data we would propose screening 6-monthly during the first post-operative year and then at 2 years. If these smears were normal, the patient could then revert to the normal screening programme.

The aim of a successful cervical cytology screening programme is to detect and treat pre-invasive cervical intraepithelial neoplasia (CIN), thereby reducing the incidence and mortality of cervical cancer (Duguid *et al.* 1985).

While CIN is a frequently encountered lesion, the histologically identical tumour in the vagina, vaginal intraepithelial neoplasia (VAIN), is rare. It has been generally assumed that the natural history of the two conditions may be similar with regard to the possible development of invasive cancer. For this reason any patient undergoing hysterectomy in association with CIN 3 (carcinoma *in situ*/severe dysplasia) has traditionally been carefully followed with frequent vault smears. Such intensive follow-up places some pressure on gynaecology clinics, general practitioner services, cytology services and, not least, the patient herself.

VAIN has been reported after hysterectomy for CIN in 0·9–6·8% (Gallup & Morley 1975; Woodruff 1965). In Tayside the cervical cytology service has been active since the early 1960s. There is good participation by a fairly homogeneous population which tends to be static and therefore lends itself to longitudinal study. We set out to determine whether the subsequent development of VAIN justified our intensive cytology follow-up after hysterectomy given the present financial constraints on the National Health Service.

This study was conducted in two parts, firstly as a retrospective longitudinal study to determine how many patients with CIN 3 treated by hysterectomy went on to develop VAIN or vaginal carcinoma and, secondly, by identifying women presenting with vaginal carcinoma to determine the number where this disease had been preceded by CIN 3.

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Subjects and methods

Women undergoing hysterectomy in the presence of CIN 3 during the years 1967–1977 in the Tayside region were identified from the gynaecology cancer register. After hysterectomy, they had been asked to attend the gynaecology clinic for vault cytology every 6 months for the first year, then annually over a 10-year period and again at 15 years.

By reviewing the cytological records it was possible to identify those women with abnormal cytology postoperatively. The time interval between surgery and the first abnormal smear was noted, together with the outcome of any abnormal cytology.

Again using the cancer register all women with vaginal carcinoma diagnosed over a 31-year period between 1957 and 1987 were identified. The records were reviewed and a previous history of carcinoma *in situ* of the cervix or vagina was noted.

Results

Between 1967 and 1977, 341 women underwent hysterectomy where the pathological diagnosis of CIN 3 had been made before, or at, hysterectomy. Their ages ranged from 22 to 66 years with a mean age at hysterectomy of 35 years. Of these 341 women, 219 (64%) completed 10 years of cytology follow-up. Of the 122 (36%) who failed to complete 10 years of follow-up, 8 (6%) had died from unrelated causes; 51 (42%) had moved from the Tayside area, 27 (22%) were known to be well but had refused further smears, 4 (3%) had been discharged from the clinic (as was the practice for those women at the age of 60 years), and 32 (26%) had been lost to follow-up (Table 1).

Of the 246 women eligible for longer follow-up, 106 (43%) are not yet eligible for 15-year smears. Of the 140 who are, 79 (56%) have completed 15 years of follow-up. Of the 61 (44%) who have failed to do so, 2 (3%) have died of unrelated causes, 4 (6%) have left the Tayside area, 16 (26%) are known to be well, but have declined further smears, 16 (26%) have been discharged from follow-up having attained 60 years of age, and 23 (38%) have been lost to follow-up (Table 2).

Of the 219 women completing 10 years of vault smears, only 8 (4%) had abnormal cytology. Of these, six had smears which reverted to normal within the 10-year period with no treatment apart from antibiotics The worst smear in this group was classified as Class 3 on a 5-point scale.

In the other two women who continued to have abnormal smears, the time interval between hysterectomy and the first abnormal smear was less than 1 year. In the first patient, excision of carcinoma *in situ* was thought to be complete at hysterectomy at the age of 28, but 10 months after surgery, her repeat smears were reported as Class 2, and vaginal vault biopsy 3 years later confirmed the presence of VAIN. In the second patient, incomplete excision of carcinoma *in situ* at hysterectomy at the age of 57 was suspected. A smear taken 7 months after surgery was reported as Class 5 and VAIN was confirmed on vaginal vault biopsy 2 months later.

A third patient initially aged 27 at hysterectomy completed 10 years of follow-up with

Table 1. Outcome of 10-year cytology follow-up in 341 women after hysterectomy in association with CIN 3

Outcome	No. of women
Completed follow-up	(n = 219) n (%)
Developed abnormal smear	8 (3·6)
Developed VAIN	2 (0·9)
Incompleted follow-up	(n = 122) n (%)
Died (unrelated cause)	8 (6·6)
Moved from area	51 (41·8)
Well (refused further smears)	27 (22·1)
Discharge (age >60 years)	4 (3·3)
Lost to follow-up	32 (26·2)

Table 2. Outcome of 15-year cytology follow-up in 140 women after hysterectomy in association with CIN 3

Outcome	No. of women
Completed follow-up	(n = 79) n (%)
Developed abnormal smears between 10 and 15 years	1 (0·1)
Developed VAIN	1 (0·1)
Incompleted follow-up	(n = 61) n (%)
Died (unrelated cause)	2 (3·3)
Moved from area	4 (6·6)
Well (refused further smears)	16 (26·2)
Discharge (age >60 years)	16 (26·2)
Lost to follow-up	23 (37·7)

normal cytology and then had a Class 2 smear at 15 years. Vault biopsy confirmed VAIN 16 years after hysterectomy.

Of these three women with a diagnosis of VAIN, the first had normal cytology for a 5-year period after treatment by 'cold' coagulation. The second underwent total vaginectomy with no evidence of further recurrence 5 years after surgery and the third, following cold coagulation, left the Tayside area and was lost to follow-up.

Retrospective study of vaginal carcinoma

During the period 1957–1987, 60 patients with vaginal carcinoma were identified from the gynaecology cancer register. Of these 60 tumours, 47 (78·3%) were primary and 13 (21·7%) were secondary neoplasms. The age of the patients ranged from 32 to 93 years with a mean age of 65·9 years (SD 15·0).

Only two women with primary vaginal carcinoma had had a previous hysterectomy and the pathology report in one of them was normal. The second woman had had a hysterectomy in 1936, 30 years before the diagnosis of vaginal carcinoma and no pathology report or blocks were available.

Of the 13 women with secondary tumours, two had had a hysterectomy. One had a hysterectomy at the age of 42 following a cone biopsy where microinvasive carcinoma of the cervix was suspected. Histological examination of the hysterectomy specimen demonstrated residual carcinoma *in situ* with incomplete clearance. Smears were performed annually thereafter over a 3-year period and all were Class I. Four years after surgery the smear was reported as Class 4 and on repeat as Class 5. Vaginal biopsy showed an undifferentiated carcinoma extending to a depth of 2 mm. The second woman had had a hysterectomy at the age of 47 after incomplete clearance of a carcinoma *in situ* by cone biopsy. Histological examination of the hysterectomy specimen showed no residual CIN. This woman presented 18 years later with a 'basaloid' carcinoma of rectum and vaginal recurrence of the rectal tumour 2 years afterwards.

Thus, of all vaginal carcinomas encountered over a 31- year period, only one occurred in association with a diagnosis of previous carcinoma *in situ* of the cervix.

Discussion

The incidence of VAIN following hysterectomy for CIN 3, amongst those women in Tayside region who completed 10 years of follow-up, was 0·91%. The natural history of this rare disease is not yet fully understood but progression to invasive malignancy has been recorded (Lee & Symonds 1976; Grahams & Meigs 1952).

Vault cytology provides a suitable and acceptable test for detection of pre-invasive disease of the vagina and therefore is indicated in the follow-up of patients undergoing hysterectomy for CIN 3. However, the question raised by this study is the value of continued frequent cytology review remembering that while smear tests are widely acceptable, they still cause considerable stress and anxiety to the woman.

In Tayside region, 219 women attended for annual review over a 10-year period. Eight of these developed abnormal smears, 75% of which reverted to normal without any active intervention. In two women the smears remained abnormal and VAIN was later diagnosed by biopsy. The large number of smears involved is evident and the cost of such intensive screening must be justified in terms of the benefit to the patient.

Of the three women who went on to develop VAIN, two did so within the first year and the third at 15 years. No woman developed invasive vaginal carcinoma. In the retrospective study of vaginal carcinoma, one woman had had a hysterectomy for carcinoma *in situ*. This occurred outside the period of the longitudinal study, ie 1967–1977. This woman developed vaginal carcinoma 4 years after hysterectomy but smears in the intervening period were entirely normal.

We have found little evidence in this study to justify screening women who have undergone hysterectomy for CIN 3 any more frequently than the general population, provided that their smears have remained negative for 2 years after surgery. Until the natural history of VAIN is better understood and the time scale for the development of invasive cancer is known, long-term cytology review is indicated and must be pursued.

We propose therefore that the follow-up of women, after hysterectomy for CIN 3 should involve smears performed 6-monthly for the first year with a third smear at 2 years. If these smears are normal, the woman could then revert to the national screening programme which at present, involves smears at 5-year intervals until the age of 60 years in Scotland or 65 years in England and Wales. It is hoped that this may be increased to 3-year intervals in the foreseeable future.

Checking of the Tayside gynaecology cancer register failed to reveal any woman in the study period whose vaginal carcinoma had been preceded by hysterectomy for CIN 1 or 2. Such women therefore require follow-up smears no more frequently than the above.

Full follow-up for 10 years involves 11 visits and 11 vaginal smears. Our recommended follow-up would involve four visits and four vaginal smears within 10 years; a saving of seven visits and smears per patient. Over this 11-year period 341 women were enrolled for hospital follow-up, extending over a 21-year period. The average total saving per annum of the proposed new follow-up of a similar population would therefore be 113 visits and smears. This represents approximately 0·3% of the total workload of the Tayside cervical cytology unit.

The main advantage of our proposals is the reassurance which the patient receives sooner from reduced surveillance. There would of course be some reduction in workload for the cytology and clerical services, but a major saving in resources must await similar findings following cone biopsies and, more recently, the wave of newer techniques for dealing with CIN by local destruction.

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The effect of maternal work on fetal growth and duration of pregnancy: a prospective study

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Summary. The effect on birth outcome of work requiring different degrees of physical exertion was examined among 15 786 pregnant women who were followed through the Guatemalan Social Security Institute's hospital. Work inside and outside the home was ascertained through a questionnaire administered to each woman before delivery. Odds ratios were adjusted for household income, maternal height and age, and birthweight of previous infant. Women with three or more children and no household help were at increased risk for small-for-gestational-age (SGA) births compared with women with family (odds ratio (OR) 1·79; 95% confidence interval (CI) 1·31, 2·47) or hired help (OR 2·0; 95% CI 1·16 to 3·33). Compared with office work, manual work increased the risk for an SGA (OR 1·32; 95% CI 1·12 to 1·56) and SGA/preterm birth (OR 2·56; 95% CI 1·10 to 5·96). Work in a standing compared with sitting position significantly increased the risk for a preterm birth (OR 1·56; 95% CI 1·04 to 2·60). There was a significant positive trend in frequency of SGA and SGA/preterm birth with an increase in the physical demands at work, as measured by an activity score. These data suggest that interventions to reduce physical exertion among pregnant women could improve birth outcome.

Although a more recent phenomenon in the middle classes of developed countries, women in lower classes in developed and developing countries have traditionally had high rates of participation in the formal and informal sectors of the economy. Invariably these women are also responsible for a wide range of household and childcare duties. These are also the women at highest risk for poor birth outcome.

The studies that have examined the relation between work and pregnancy outcome have yielded conflicting results (Chamberlain & Garcia 1983) that reflect differences in working conditions across study populations or over time (Saurel-Cubizolles & Kaminski 1986), and some problems of definition and method.

Four important pitfalls affect the interpretation of studies on the effect of maternal work on birth outcome. In some reports (Gofin 1979; Algre *et al.* 1984; Marbury *et al.* 1984; Peters *et al.* 1984), work during pregnancy has been defined narrowly as formally employed or not; this definition does not capture the full range of, and differences in, women's work activities

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(Mamelle *et al.* 1984). The studies that have attempted to refine the definition of work to describe characteristics that may have a physiological impact on pregnancy (Naeye & Peters 1982; Murphy *et al.* 1984) have done so on a *post hoc* basis using standard occupation definitions rather than obtaining a description directly from the women.

Although working and non-working women, and women within the work force have been shown to differ in ways that may affect birth outcome (Chamberlain & Garcia 1983), many reports have not adequately taken these differences into account in their analyses (Algre *et al.* 1984; Peters *et al.* 1984; Stewart 1955; Tafari *et al.* 1980).

Finally, although a few studies (Marbury *et al.* 1984; McDonald *et al.* 1988; Saurel-Cubizolles & Kaminski 1987) have distinguished birth outcome by the gestational age and birthweight categories known to be different epidemiological and clinical entities (Villar *et al.* 1986), only one (Peters *et al.* 1984) has distinguished between term and preterm small-for-gestational-age infants; global analyses might mask the effect of work on birth outcome.

Here we examine the association between birth outcome and work among a large cohort of pregnant women from a low to middle class urban population in Guatemala City, Guatemala. This analysis was designed to examine the joint and net effects on birth outcome of both housework and formal employment. We expected an increase in the risk for poor birth outcome as the physical demands from work inside or outside the home increased. To test this hypothesis we compared those: (i) with different household loads, (ii) formally employed and not employed, and (iii) formally employed and working under different conditions.

Subjects and methods

This is a prospective follow-up study designed to study risk factors associated with small-for-gestational-age (SGA) infants and preterm delivery. The sample included all pregnant women (n = 16 850) who had their first prenatal visit between April 1984 and January 1986 at the antenatal clinic of the Gynecology and Obstetrics Hospital of the Guatemalan Social Security Institute (IGSS) in Guatemala City. Women were eligible for social security benefits, including hospital care, either because they or their husbands were formally employed. This is a relatively healthy population with evidence of some chronic malnutrition. A detailed description of the population has been presented elsewhere (Kestler *et al.* 1987).

The subject of this analysis is 15 786 pregnant women. We excluded from the total sample 154 sets of twins, 169 infants born with major congenital malformation, and 587 cases with missing data on the variables of interest.

Socio-demographic, obstetric, nutritional and work data used in this study were collected prospectively by questionnaire or clinical examination under strict standardization and quality control procedures (Kestler *et al.* 1987; Villar *et al.* 1988). At the first prenatal visit (baseline) a hospital social worker administered a questionnaire specially designed to obtain a description of work during pregnancy. If there were missing data on this baseline questionnaire then it was readministered on the postpartum ward by a study interviewer. Fourteen women reported a change in work during pregnancy; the data from their first job were used.

Housework was measured in terms of who helped the woman with her chores (no chores, paid help, family help, or no help) and how many children she had at the time of the interview. Since estimates of the association between no household chores and birth outcome were unstable because of the small number of women who reported no chores ($n = 210$), we do not present them in the housework analyses. We categorized the number of children in the household ($\leqslant 2$ *vs* $\geqslant 3$) on the basis of a report by Papiernik & Kaminski (1974) who found an adverse effect of domestic work on birth outcome among women with three or more children.

Employment was defined as participation in the formal sector and characterized by type (office or manual work), position (sitting, standing, or walking), level of physical intensity (sedentary, moderate, or intense), and number of hours worked. A wide range of combinations characterized the jobs these women held. Typically the employed women worked as store clerks, civil servants, housekeepers, secretaries, nurses, teachers, or worked in light industry such as food or clothing. A few were professionals or students. Those not formally employed (unemployed) may have worked in the informal sector as sellers, childminders, or in home industry.

Birthweight and gestational age by newborn physical examination (Capurro *et al.* 1978) were assessed immediately after birth by trained neonatology nurses using standard methods (Villar *et al.* 1988). In cases where the newborn physical examination data were missing, last menstrual period was used to calculate gestational age ($n = 528$).

Newborns classified as: (1) Normal birthweight term infants (the reference group) were ≥37 weeks gestational age and weighed >10th centile for gestational age of a sex-specific standard from a well-nourished population (Williams *et al.* 1982); (2) SGA/preterm infants were <37 weeks and weighed ≤10th centile; (3) preterm infants were <37 weeks and weighed >10th centile; and (4) SGA infants were ≥37 weeks and weighed ≤10th centile.

In preliminary analyses followed by multivariate logistic (SAS 1986) and multinomial logistic (Cox 1970; SAS 1985) regression we compared birth outcomes of women with different types of work. The regression models were adjusted for maternal age (<20, 20–34, 35+ years), monthly household per capita income (</≥75th centile), maternal height (</≥147 cm) and birthweight of the previous infant (nulliparous, </≥2.5 kg). These four out of the many demographic, economic, nutritional and obstetric factors that were potential confounding variables were selected because they were significant determinants of at least one birth outcome and were not highly correlated with each other. Although pre-pregnancy weight was also a significant covariate it was not included in the final model because there were data on only 13 437 women. However, when pre-pregnancy weight was studied in this subsample, the relations between work and birth outcome were the same as in the larger sample. To test the differential effect of work in subgroups of the population we examined the interactions between covariate and work variables.

Three different analyses are presented: the first tested the association between types of household work and birth outcome; the second examined the association between formal employment and birth outcome, net of and jointly with household work. Joint effects were tested with interaction terms; if an interaction was significant for any one birth outcome, analyses for that outcome were stratified by one of the variables. Finally, we examined the association between different conditions of formal employment and birth outcome. To summarize the joint effect on birth outcome of type, position, physical intensity level, and number of hours of work we developed an activity score. This birth outcome-specific score is the sum of the adjusted odds ratios associated with each working condition that characterized a woman's work. Women were classified on the basis of their activity score into minimum, low, moderate or high groups. The minimum level included those who sat while performing office work that was essentially sedentary. The high level included those who, for >40 h, stood or walked at manual work that was moderate/intense in physical intensity. A linear test for trend was used to measure the association between the incidence of a birth outcome and the activity score (Fleiss 1981).

Results

At birth, normal term infants ($n = 12\,061$) had a mean weight of 3·26 (SD 0·33)kg and mean gestational age of 39·4 (SD 0·7) weeks; SGA infants ($n = 3250$) weighed 2·59 (SD 0·24)kg at gestational age 39·3 (SD 0·9) weeks; preterm infants ($n = 368$) weighed 2·28 (SD 0·65)kg at gestational age 33·9 (SD 2·7) weeks; and SGA/preterm infants ($n = 107$) weighed 1·64 (SD 0·47)kg at gestational age 34·7 (SD 1·6) weeks. Table 1 describes the distribution of these birth outcomes within housework and employment groupings that represent the different aspects of work examined in subsequent analyses.

Table 1 shows that 20% of the women had household help and 33% were employed. A higher percentage of working women had household help than did unemployed women (44% of office workers, 34% of manual workers and 12% of unemployed). Of those employed, 36% performed work mostly in a sitting position and 17% reported their job was essentially sedentary.

In the crude data (Table 1), women who had hired help at home had a significantly ($P<0·0001$) lower proportion of SGA births and higher proportion of preterm births than women with family help or no help with household chores. Women with family help had significantly ($P<0·01$) more SGA/preterm births than women with hired or no help at home Women in office work had a significantly ($P<0·0001$) lower proportion of SGA births than manual workers and unemployed women; women in manual work had a significantly higher proportion of SGA/preterm births ($P<0·01$) than the others.

Table 1. The relation between birth outcome and type of work among women from Guatemala City, 1984–1986

Work characteristics	*n*	Birth outcome* (%) SGA	SGA/ preterm	Preterm
Household help†				
None	12 341	21·27	0·60	2·32
Family	2192	19·48	1·14§	1.87
Hired	1043	14·96‡	0·67	3·74§
Type of formal work				
Not formally employed	10 568	21·22	0·61	2·16
Office	1700	16·80‡	0·41	2·88
Manual	3518	20·81	1·02§	2·59
Position of work				
Sitting	1877	17.16§	0·59	2·29
Standing	1815	20·39	0·77	3·14
Walking	1526	20·64	1·18	2·62

* Normal birth outcome constitute remaining portion of births.

† Data on 210 women reporting no household chores are not shown.

‡ χ^2, $P<0{\cdot}0001$ within birth outcome group, proportion significantly different from the other two levels.

§ χ^2; $P<0{\cdot}01$ within birth outcome group, proportion significantly different from the other two levels.

Women who worked in a sitting position had a significantly ($P<0{\cdot}0001$) lower proportion of SGA births than women who stood or walked at work. No significant relation between position of work and preterm or SGA/preterm birth outcome was detected.

Table 2 describes the same selected housework and employment groups by the four covariates used to adjust the multivariate regression models. Within categories of work, the women with the highest income, who were the oldest and tallest, and who had the lowest percentage of previous low birthweight were those who had hired help for chores, who had office work, who sat, or who had sedentary jobs (physical intensity data not shown). Conversely women with no household help, who were unemployed, who walked at work, and who were engaged in physically intense work had the lowest incomes and the highest percentage of previous low birthweight. Women with ≤2 and ≥3 children did not differ in any characteristics measured by the covariates, maybe because they had not yet completed their childbearing.

Table 3 presents the adjusted odds ratios for the association between housework and birth outcome. Women with three or more children had a significantly higher risk for SGA than women with two or fewer children. Number of children modified the effect of household help on SGA (interaction of family help and number of children: $P = 0{\cdot}0009$; and for hired help and number of children: $P = 0{\cdot}04$). This interaction is significant even though the group of women with ≤2 children included nullipara, who gave birth to proportionately more SGA than multipara (26% *vs* 19%). The stratified analysis for SGA and household help by number of children is shown in the bottom half of Table 3. Among women with three or more children, those with no household help had a significantly higher risk for SGA than women with family help (OR 1·79; 95% CI 1·31 to 2·47) or with hired help (OR 2·00; 95% CI 1·16 to 3·33).

On the other hand, women assisted by family help had significantly higher odds for a SGA/preterm birth than those with no household help at home (Table 3). However, the women with family help had higher rates of morbidity during pregnancy than women with no help (hospital admission during pregnancy: 18% without help, 36% with family help; infection: 8% without help, 16% with family help; haemorrhage: 1% without help, 4% with family help).

The association between formal employment and birth outcome is presented in Table 4. No effect of employment status on preterm birth was observed. Women engaged in manual work had significantly higher odds for a SGA/preterm birth than unemployed women (OR 1·68; 95% CI 1·08 to 2·60). Again analyses for SGA were stratified by number of children (interaction between manual work and number of children $P = 0{\cdot}0014$; interaction between office work and number of children ($P = 0{\cdot}03$). There were reduced odds for SGA among office and manual workers with three or more children and among office workers with two or fewer children. Adjustment for household help reduced slightly this protective effect of work on SGA among employed women with three or more children. This suggests that the association between employment and SGA is not independent of household work among women with three or more children, who probably had the most work.

The associations between different working conditions and birth income are shown in Table 5. Odds for SGA were significantly higher

Table 2. Socio-demographic, obstetric and nutritional description of the women by working condition: Guatemala City, 1984–1986

Work characteristics	*n*	Monthly income (Q)*	Maternal age (years)	Maternal height (cm)	Previous low birthweight ≤2500 g (%)
Household help†					
None	12 341	71 (87)	25·1 (1·3)	152·2 (6·6)	10·6
Family	2192	85 (65)	25·7 (6·1)	152·8 (6·9)	9·5
Hired	1043	129 (90)	27·3 (5·0)	155·3 (6·4)	7·9
Type of formal work					
Not formally employed	10 568	60 (45)	25·0 (5·6)	151·9 (6·6)	10·6
Office	1700	153 (92)	26·4 (4·7)	155·5 (6·5)	8·5
Manual	3518	93 (20)	26·1 (5·2)	152·8 (6·7)	9·7
Position of work					
Sitting	1877	136 (92)	26·0 (4·8)	154·7 (6·7)	8·9
Standing	1815	101 (67)	26·1 (5·2)	152·9 (6·6)	9·2
Walking	1526	99 (67)	26·5 (5·3)	153·4 (6·8)	11·4

Results are means (SD).

* 1 Guatemalan Quenzales = US$1.00 in 1984.

† Data on 210 women reporting no household chores are not shown

among women in manual compared with office jobs (OR 1·32; 95% CI 1·12 to 1·56), and among those who stood (OR 1·21; 95% CI 1·02 to 1·44) and walked (OR 1·28; 95% CI 1·07 to 1·53) compared with those who sat. Similarly, risk for SGA/preterm was significantly higher among women who worked in manual jobs compared with those in office jobs (OR 2·56; 95% CI 1·10

Table 3. The effecct of household work on birth outcome: adjusted* odds ratios (95% CI), Guatemala City, 1984–1986

	Birth outcome†			
Household work	SGA (*n* = 3250)		SGA/preterm (*n* = 107)	Preterm (*n* = 368)
No. of children alive				
≤2	1·0		1·0	1·0
≥3	1·17 (1·04–1·31)		1·34 (0·75–2·41)	1·22 (0·89–1·66)
	No. of children alive ≤2 (*n* = 2667)	≥3 (*n* = 583)		
Household help‡				
Family help	1·0	1·0	1·0	1·0
None	1·03 (0·91–1·18)	1·79 (1·31–2·47)	0·56 (0·43–0·89)	1·35 (0·97–1·89)
Hired help	1·0	1·0	1·0	1·0
None	1·15 (0·95–1·41)	2·00 (1·16–3·33)	0·85 (0·38–1·89)	0·72 (0·51–1·04)

* Odds ratios adjusted for covariates: monthly per capita income, maternal age and height, and birthweight of previous infant.

† Reference is normal birthweight group: *n* = 12 061.

‡ Excludes *n* = 210 who reported no household chores· SGA *n* = 42; SGA/preterm *n* = 1; preterm *n* = 2; normal birth *n* = 165.

Table 4. The effecct of formal employment on birth outcome: adjusted* odds ratios (95% CI), Guatemala City, 1984–1986

Type of formal work	Birth outcome† SGA (*n* = 3250)		Birth outcome† SGA/preterm (*n* = 107)	Birth outcome† Preterm (*n* = 368)
	No. of children alive ≤2 (*n* = 2667)	 ≥3 (*n* = 583)		
Unemployed	1·0	1·0	1·0	1·0
Office				
Without adjustment for household help‡	0·80 (0·68–0·94)	0·38 (0·18–0·81)	0·63 (0·27–1·46)	1·01 (0·71–1·44)
With adjustment for household help	0·81 (0·69–0·96)	0·48 (0·22–1·01)	0·54 (0·23–1·27)	1·05 (0·73–1·52)
Manual				
Without adjustment for household help	1·05 (0·94–1·18)	0·67 (0·51–0·87)	1·68 (1·08–2·60)	1·08 (0·83–1·41)
With adjustment for household help	1·07 (0·96–1·19)	0·76 (0·58–0·99)	1·50 (0·96–2·37)	1·12 (0·85–1·46)

* Odds ratio adjusted for covariates: monthly per capita income, maternal age and height, and birthweight of previous infant.

† Reference is normal birthweight group: *n* = 12 061.

‡ Household help = yes/no.

to 5·9) and higher among women who walked compared with those who sat at work (OR 2·07; 95% CI 0·96 to 4·47). Women who stood at work were at significantly higher risk for a preterm birth than women who sat (OR 1·56; 95% CI 1·04 to 2·60).

The frequency of SGA, SGA/preterm, and preterm by activity score is shown in Fig. 1. Overall the relation between SGA and activity level was a U-shaped curve with a significant dip in proportion of SGA births among women in jobs with low physical demands (Fig. 1). There was a significant positive linear trend in proportion of SGA/preterm births by activity score

Table 5. The effect of working conditions on birth outcome among employed women: adjusted* odds ratios (95% CI), Guatemala City, 1984–1986

Characteristics of formal work	Birth outcome† SGA (*n* = 1007)	Birth outcome† SGA/preterm (*n* = 43)	Birth outcome† preterm (*n* = 140)
Type			
Office	1·0	1·0	1·0
Manual	1·32 (1·12–1·56)	2·56 (1·10–5.96)	1·11 (0·77–1·62)
Position			
Sitting	1·0	1·0	1·0
Standing	1·21 (1·02–1·44)	1·31 (0·58–2.93)	1·56 (1·04–2·6)
Walking	1·28 (1·07–1·53)	2·07 (0·96–4 47)	1·33 (0·85–2·08)

* Odds ratio adjusted for covariates: monthly per capita income, maternal age and height, and birthweight of previous infant.

† Reference is normal birthweight group: *n* = 4028

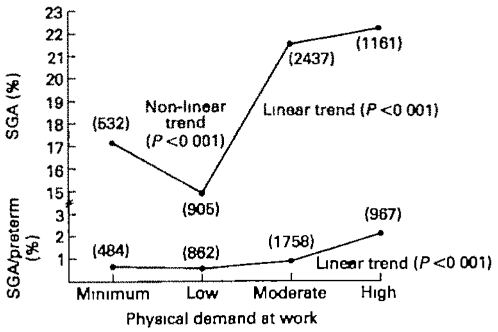

Fig. 1. The effect of physical demand at work during pregnancy on fetal growth and duration of gestation. Minimum activity, office work that was sedentary and performed in a sitting position High level· manual work, at a moderate or intense level, walking or standing, for >40 h a week.

($P<0{\cdot}002$) with the highest proportion of SGA/preterm births being born to women who had high physical demands, and the lowest being born to women with minimum to low physical demands. There was a positive, but not significant trend in preterm births with increased physical demand at work (minimum = 3·09%; high = 4·56%).

Discussion

The quality of the data from this study has been reported previously. There was excellent agreement for newborn anthropometry and gestational age as well as for the questions on whether or not a woman was formally employed and whether or not she had help at home. There was fair agreement for questions on position at work (seated/standing *vs* other) and number of hours worked per week (Villar *et al.* 1988).

Like others (Gofin 1979; Manshande *et al.* 1987), we found that high levels of physical demand both at home and in the workplace adversely affected birthweight. Both our study and that of Papiernik & Kaminiski (1974) found that women with three or more children and no domestic help were most vulnerable to poor pregnancy outcome. In their study, women with three or more children at home had proportionately more infants born ≤35 weeks and ≤2000 g, some of whom would have been classified as SGA/preterm in our study. In our population women with no household help and three or more children were at significant risk of giving birth to SGA infants. Household help therefore promises to be an effective intervention to reduce SGA among those with the highest burden of housework: those with three or more children. Our analyses also reinforce the approach that housework be taken into consideration in any analysis of the effect of formal employment on birth outcome.

Even after adjusting for household help, employed women, particularly office workers, still had marginally lower odds for a SGA birth than unemployed women. Two explanations have been offered for better reproductive performance among workers (Murphy *et al.* 1984; Saurel & Kaminski 1983). One is that workers have available to them health care and information that are not available to unemployed women. Since all the women in the study had equal access to the hospital's services, and there were no significant differences in number of prenatal visits among the employed and unemployed, this explanation is less likely. Another is that women who work are healthier than those who do not (known as the healthy worker effect) (Joffe 1985); this may be particularly so for women who both work and have three or more children. Data in Table 2 show that the employed women were better off than the unemployed, and although we have adjusted for some differences, there may be others we have not captured in our measurements.

To understand better the effect of work on birth outcome, we examined in more detail the relation between birth outcome and different levels of physical exertion (Tables 4 and 5). Those women working under physically demanding conditions were at increased risk for SGA, but our analyses, like those of Berkowitz (1981), suggest that the relation between physical demand and SGA may not be linear and that some activity is beneficial to birth outcome.

The odds of 1.56 for preterm birth associated with standing compared to sitting at work are similar to those obtained by Mamelle *et al.* (1984), although with this exception, we found very little effect of household and working conditions on risk for preterm delivery. This agrees with the findings of Berkowitz *et al.* (1983) but is at variance with other studies that have found an association between a composite activity score and preterm birth (Mamelle *et al.* 1984; McDonald *et al.* 1988). However, those authors included in their preterm group all infants of gestational age <37 weeks, regardless of birthweight; in our study we separated those born preterm from those born preterm and SGA, and we found a consistently strong association between physically demanding work and SGA/preterm outcome.

Manual workers had significantly higher odds for a SGA/preterm birth than unemployed women, despite the fact that they were better off (Table 2); they also had a significantly higher risk for SGA/preterm than office workers. For each of the comparisons of a more *versus* less physically demanding work condition, the odds ratio was greater than 1. Furthermore, with an increase in the physical demands of work, measured by the activity score, there was a significant positive increase in the proportion of SGA/preterm births. These findings are particularly important because SGA/preterm infants had the poorest outcomes in this (J. Villar, unpublished observations) and other populations (Williams *et al.* 1982).

Although each of the odds ratios comparing outcomes among workers in high and low physically demanding jobs may represent a causal relation, each may also result from selection bias of better-off women into less physically demanding jobs (Joffe 1985). Certainly the data in Table 2 show that workers who sat and who had office jobs were better off than the women with other types of jobs, differences we have attempted to control for.

The mechanisms that mediate the relation between physical aspects of work and birth outcome require further investigation. Several have been suggested and explored, including energy balance (Subcommittee on Maternal and Infant Nutrition in Developing Countries 1984; Lawrence *et al.* 1985) and uteroplacental perfusion. Strenuous movement may divert blood from the fetoplacental unit to the active muscles, or standing may reduce venous return and consequently blood volume (Morris *et al.* 1956; Tafari *et al.* 1980; Naeye & Peters 1982; Hytten 1984). It is possible that the effect of work on birth outcome is partially mediated through maternal morbidity, a question that we are now exploring. We are also exploring the likely possibility that the factors mediating the effect of work differ for SGA/preterm and SGA birth.

We have examined the effect of work on birth outcome from several different aspects, all of which consistently suggest that some types of work are associated with an adverse effect on fetal growth and duration of pregnancy. Particular groups of women that are at risk for adverse effects of work on birth outcome include those with three or more children with no domestic help and workers in physically demanding jobs. Indeed women of traditional societies have long expressed the belief that pregnant women should exercise daily to keep the woman strong, the fetus small and the labour brief (Jimenez & Newton 1979).

Future studies should focus on measuring more precisely physical activity and stress. However, on the basis of these findings we recommend that targeted intervention at the workplace be instituted to reduce physical demands on pregnant women. Furthermore, social support programmes should offer rest or household help to women with the highest household loads.

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Maternal thyroid hormones and outcome of pre-eclamptic pregnancies

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Summary. Plasma concentrations of total and free thyroxine (TT4 and FT4), total and free triiodothyronine (TT3 and FT3), thyroid-stimulating hormone (TSH), plasma albumin and urate were measured in 39 proteinuric pre-eclamptic patients presenting before labour. Pre-eclamptic patients had significantly lower FT4 and higher TSH concentrations compared with values in third trimester normotensive pregnancies. There was a significantly higher frequency of lower TT4, TT3 and high TSH levels in the subgroup of pre-eclamptic patients who had low-birthweight babies. Thyroid hormone concentrations were not correlated with gestation at delivery or birthweight but, with the exception of FT4, were correlated with plasma albumin and urate concentrations. Plasma TSH correlated with birthweight and with plasma urate. The results suggest that mild biochemical hypothyroidism may be found in proteinuric pre-eclampsia, and the concentrations of TT4, TT3, FT3 and TSH may reflect the severity of pre-eclampsia.

Patients with severe systemic illness and starvation often have low plasma triiodothyronine (T3) concentration in the presence of normal or even raised plasma thyroxine (T4) concentration (Cavalieri & Rapoport 1977). This condition, known as the low T3 syndrome, has also been noted in pre-eclampsia (Osathanondh *et al.* 1976; Tolino *et al.* 1985). We investigated thyroid function in 24 proteinuric pre-eclamptic patients (Lao *et al* 1988) and found that plasma concentrations of total thyroxine (TT4) and free thyroxine (FT4) were significantly lower and concentrations of thyroid-stimulating hormone (TSH) significantly higher compared with a gestation-matched control group. Furthermore, TT4, FT4, total triiodothyronine (TT3) and free triiodothyronine (FT3) concentrations were lower and TSH concentration was higher in the patients who gave birth to small-for-gestational-age babies. We have now extended the study and examined the relation between thyroid hormones, TSH, and the outcome of 39 pre-eclamptic pregnancies.

Patients and methods

Thirty-nine proteinuric pre-eclamptic patients presenting before labour were studied. Pre-eclampsia was diagnosed in hospital when the blood pressure was ≥140/90 mmHg on two or more occasions at least 6 h apart Proteinuria was diagnosed by a dipstix reading of ≥1+ in repeated clean-catch midstream urine samples. None of the pre-eclamptic patients had clinical

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Table 1. Concentration of thyroid hormones in pre-eclamptic and normotensive women

	Pre-eclamptic patients (n=36–39)		Normotensive women† (n=24)	
Hormone	Mean (SD)	Range	Mean (SD)	Range
TT4 (nmol/l)	118·8 (27·0)	60–195	131·6 (23·2)	106–187
FT4 (pmol/l)	12·5 (4·4)*	4·3–26·7	16·3 (4·4)	9·2–27·8
TT3 (nmol/l)	1·9 (0·7)	0·9–4·5	2·1 (0·5)	1·4–2·9
FT3 (pmol/l)	2·8 (1·2)	0·4–5·9	3·3 (0·8)	2·0–5·4
TSH (miu/l)	3·9 (1·9)**	1·0–12·3	2·5 (0·8)	1·0–5·2

*$P<0{\cdot}01$

**$P<0{\cdot}001$.

†Values obtained in normotensive third trimester pregnancies (Lao *et al.* 1988).

features of thyrotoxicosis or was taking medication that might affect thyroid function.

After pre-eclampsia was diagnosed, 10 ml of venous blood were collected and sent to the laboratory in a heparinized plastic tube. The plasma was separated as soon as possible and stored at −20°C. Plasma TT4 was measured by an enzyme multiplied method (SYVA EMIT) adapted for use on the Cobas-Bio centrifugal analyser. Plasma FT4, TT3, FT3 and TSH were measured by radioimmunoassay using commercial kits from Diagnostic Product Corporation. Plasma was also estimated for albumin and urate concentrations.

The concentrations of thyroid hormones in the pre-eclamptic women are compared with values in normotensive third trimester pregnancies reported previously by Lao *et al.* (1988). Patients with low-birthweight infants (<2·5 kg) and preterm delivery (<37 weeks) were compared by Fisher's exact test. Student's *t*-test was used for other analysis.

Results

Six of the 39 pre-eclamptic patients were multiparous (parity 1–4). The mean gestation at blood sampling was 37·2 (SD 2·5) weeks, and 32 of them were delivered within 7 days of admission; the rest within 2 weeks. The concentrations of thyroid hormones are shown in Table 1. Compared with values in third trimester normoten-

Table 2. Relations between thyroid hormone concentrations and gestation at delivery or birthweight

		Gestation at delivery (weeks)		Birthweight (g)	
Hormone	n	<37	≥37	<2500	≥2500
TT4 (nmol/l)					
<106	11	5	6	7***	4
≥106	28	5	23	5	23
FT4 (pmol/l)					
<9·2	9	3	6	4	5
≥9·2	27	5	22	5	22
TT3 (nmol/l)					
<1·4	8	3	5	5*	3
≥1·4	28	5	23	5	23
FT3 (pmol/l)					
<2·0	7	2	5	3	4
≥2·0	29	6	23	7	22
TSH (miu/l)					
<5·2	33	5	28	7	26
≥5·2	3	3***	0	3**	0

Fisher's test *$P<0{\cdot}03$, **$P<0{\cdot}02$, ***$P<0{\cdot}01$

Table 3. Correlation between thyroid hormone concentrations, gestation at delivery, birthweight, plasma albumin and urate concentrations.

	Correlation coefficient (r) for				
	TT4	FT4	TT3	FT3	TSH
Gestation at delivery	0·146	−0·027	0·288	0·109	−0 244
Birthweight	0·161	−0·024	0·344	0·282	−0·359*
Albumin	0·543**	0·388	0·777****	0·715****	−0·272
Urate	−0·403*	−0·072	−0·532***	−0·496**	0·440*

t-test *$P<0{\cdot}05$, **$P<0{\cdot}02$, ***$P<0{\cdot}01$, ****$P<0{\cdot}001$.

sive women, the pre-eclamptic patients had significantly lower FT4 ($P<0{\cdot}01$), and significantly higher TSH ($P<0{\cdot}001$), while TT4, TT3 and FT3 concentrations were slightly but not significantly lower.

The proportion of pre-eclamptic patients who had thyroid hormone concentrations below the range found in normal pregnant women varied, the percentages being 28·2% (11/39), 25% (9/36), 22·2% (8/36), and 19·4% (7/36) for TT4, FT4, TT3 and FT3 respectively. TSH concentration was higher in 8·3% (3/36) of pre-eclamptic patients. The pre-eclamptic patients were divided into two subgroups according to whether their thyroid hormones and TSH concentrations were within the normal range or not and the subgroups were compared as to the outcome of pregnancy (Table 2). There was a higher frequency of low thyroid hormone concentrations in patients who were delivered before 37 weeks, being 50% (5/10), 37·5% (3/8), 37·5% (3/8) and 25% (2/8) for TT4, FT4, TT3 and FT3 respectively, but the difference was not statistically significant (Table 2). However, all three patients with higher than normal TSH concentration were delivered before 37 weeks ($P=0{\cdot}008$). A significantly higher proportion of patients with low TT4 and TT3 were delivered of low-birthweight babies (Table 2), and all three patients with high TSH levels had low-birthweight babies.

Birthweight was not correlated with any of the thyroid hormones but there was a significant correlation with TSH ($P<0{\cdot}05$) (Table 3). There was no significant correlation between gestation at delivery and any of the thyroid hormones or TSH. TSH did not correlate with any of the thyroid hormones, but was correlated with plasma urate concentration. The thyroid hormones, except FT4, were found to be positively correlated with plasma albumin and negatively correlated with plasma urate concentrations.

Discussion

In non-pregnant patients with non-thyroidal illness, FT4 is often in the normal range while TT3 and TT4 are low (Chopra *et al.* 1983; Pearce & Byfield 1986). The mechanism of this 'low T3 syndrome' is thought to be a decrease in the peripheral conversion of T4 to T3 (Cavalieri & Rapport 1977). Our present results confirm the changes in thyroid hormones in pre-eclampsia described by Lao *et al.* (1988), but which are unlike those described for the low T3 syndrome (Cavalieri & Rapport 1977; Osathanondh *et al.* 1976; Tolino *et al.* 1985). Moreover, although FT4 and FT3 levels fall towards the end of normal pregnancy (Smith & Bold 1983; Franklyn *et al.* 1983), 25% and 19% of our pre-eclamptic patients respectively had lower FT4 and FT3, and 8·3% had higher TSH concentrations than was found in normal pregnant controls. This suggests the presence of mild hypothyroidism in our pre-eclamptic patients. Although thyroid antibodies were not measured in our pre-eclamptic patients, we do not think that any of them had autoimmune hypothyroidism because the highest TSH value was only 12·3 miu/l and all of them were normal when examined at their postnatal visits.

Nevertheless, controversies exist about the mechanism and significance of low concentrations of free thyroid hormones measured by commercial kits. Recent studies suggest that the measurement of free thyroid hormones using radioimmunoassay with analogue kits tends to give low results in non-thyroidal illness and is related to the decreased plasma albumin concentrations in these patients (Liewendahl *et al.* 1984; Csako *et al.* 1987). The significant correlation between plasma albumin and FT3 concentrations observed in our study suggests that disturbed plasma albumin concentration could be responsible for the lowered FT3 concentrations, but there was no correlation between FT4 concentration and albumin. Thus hypoalbuminaemia is unlikely to account for a decreased concentration of FT4 which, together with a significantly higher TSH concentration, suggests the presence of genuine hypothyroidism.

Although there was no correlation between any of the thyroid hormones and birthweight or gestation at delivery, the patients with low TT4 and TT3, as well as high TSH concentration, tended to have low-birthweight babies. The findings therefore suggest that low TT4 and TT3 reflect the severity of pre-eclampsia. The significant correlations between TT4, TT3 and FT3 with plasma albumin and urate concentrations are further evidence that thyroid hormones reflect the severity of pre-eclampsia, since low birthweight was related to low serum albumin (Studd & Blainey 1969) and serum albumin was reduced in proteinuric pre-eclampsia (Studd *et al.* 1970), while hyperuricaemia reflects the severity of fetal involvement in pre-eclampsia (Redman *et al.* 1976). The correlation between plasma urate and TSH concentration also suggests that the state of biochemical hypothyroidism is related to pre-eclampsia.

The results of our study suggest that the disturbances in thyroid hormone concentrations appear to reflect the severity of pre-eclampsia, and another study looking at serial changes in thyroid hormones in pre-eclampsia is now in progress in our hospital.

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Large intrauterine haematomata in threatened miscarriage. Frequency and clinical consequences

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Summary. Previously we described intrauterine haematomata seen with ultrasound in patients with threatened miscarriage and we suggested that a haematoma of ⩾50 ml might represent a risk to the pregnancy. We have now investigated 566 patients with vaginal bleeding in the first half of pregnancy and followed up 23 (4%) who had a haematoma of ⩾50 ml (mean 71 ml, range 50–150) at between 12 and 20 weeks gestation. One patient had a miscarriage and two had a preterm delivery, so that, contrary to our original suggestion, these large haematomata do not seem to represent any serious threat to the pregnancy.

We reported previously that ultrasound scanning in patients with vaginal bleeding in early pregnancy and a live fetus occasionally revealed an intrauterine echo-free area between the membranes and the uterine wall (Mantoni & Pedersen 1981). The typical course was that the area gradually diminished in size while the patient experienced intermittent painless vaginal bleeding, and by week 24 the area had disappeared. We therefore assumed that what we had been observing was blood, and adopted the term intrauterine haematoma. We had collected from two hospitals a series of 10 patients with intrauterine haematoma; seven of them had a haematoma <50 ml and they had a successful outcome of pregnancy, whereas of the other three patients with lesions ⩾50 ml, two miscarried and the third had a preterm delivery. In spite of the very small numbers we considered that a large haematoma might represent a risk to the pregnancy (Mantoni & Pedersen 1981).

We have now investigated prospectively a series of 23 patients with threatened miscarriage and an intrauterine haematoma of ⩾50 ml, and we report on the clinical course and outcome of these pregnancies.

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Patients and methods

In the period 1 January 1980 to 1 January 1988 a total of 566 patients admitted with vaginal bleeding at between 6 and 20 weeks gestation was shown to have a live fetus on ultrasound examination. If an intrauterine haematoma was observed, it was recorded on 100-mm film, and the volume was estimated by the formula length × width × thickness × 0·5. Patients with a haematoma were offered repeat scans at 1–2 week intervals, until the haematoma had disappeared. During the first 52 months of the study the ultrasound examinations used a static scanner (Philips SonoDIAGNOST B) and thereafter a Picker LSC 7000 dynamic scanner. Gestational age was estimated by ultrasound, crown-rump length or biparietal diameter. All ultrasound examinations were performed by one of the authors (J.F.P.).

Results

A haematoma measuring ⩾50 ml was observed in 23 (4%) of 566 patients admitted with bleeding in the first half of pregnancy (Table 1). Figure 1 shows the size of the haematomata as a function of gestational age. In three patients the haematoma did not increase in size after admission, 15 patients had a haematoma <50 ml at admission, which reached its maximum size of ⩾50 ml within 1–5 weeks, and five patients had a

Table 1. Clinical characteristics in 23 patients with threatened miscarriage and a subchorionic haematoma ≥50 ml

Patient no.	Maternal age (years)	GA and size of haematoma				GA and weight at birth or miscarriage	
		On admission		At maximum size			
		GA (weeks)	Size (ml)	GA (weeks)	Size (ml)	GA (days)	Weight (g)
1	27	12	10	15	60	253	2600
2	32	18	150	18	150	254	3150
3	33	12	0	13	50	282	4000
4	29	15	25	15	55	279	3700
5	23	13	20	17	100	273	3350
6	30	13	0	14	50	279	3400
7	22	14	0	18	55	254	2880
8	23	13	70	13	70	203*	1425
9	37	12	36	15	90	269	3900
10	37	13	6	15	50	281	3810
11	36	12	7	19	50	182*	830
12	17	17	65	17	65	292	3920
13	28	13	0	14	50	289	3600
14	32	15	22	17	60	276	2750
15	27	11	22	16	50	270	3300
16	21	14	0	19	95	279	3100
17	36	9	12	13	80	299	3350
18	41	15	80	16	95	280	3770
19	24	12	38	13	50	264	3400
20	29	12	50	13	55	143†	400
21	27	12	25	15	55	291	4000
22	24	12	20	17	145	280	3500
23	28	11	30	12	60	255	2750

GA, Gestational age.
* Preterm delivery.
† Miscarriage

normal ultrasound examination on admission but developed a haematoma ≥50 ml within 1–5 weeks. All haematoma ≥50ml occurred in weeks 12–20 (Table 1) and the average maximum size was 71 ml (range 50–150). Of the 23 women, one (4%; 95% CI 0 to 22%) had a miscarriage and two (9%; 95% CI 1 to 28%) had a preterm delivery (<36 weeks), and one of the two babies did not survive.

Discussion

Our original suggestion that a large haematoma might represent a risk to the pregnancy (Mantoni & Pedersen 1981) seemed plausible because a large haematoma could irritate the uterus and induce miscarriage or preterm delivery, but apparently it is not so. Since the size of a haematoma represents the difference between concealed and revealed bleeding, its size does not indicate the severity of the bleeding and is therefore not of central importance.

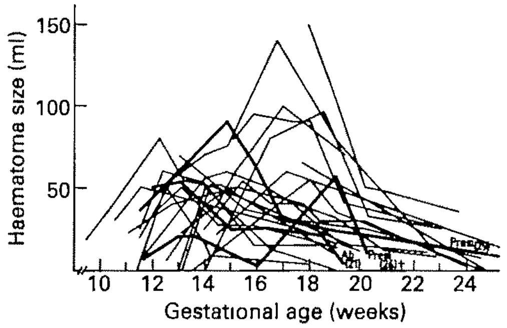

Fig. 1. Time course of estimated volume of haematoma in 23 women with vaginal bleeding between 6 and 20 weeks and an intrauterine haematoma of a maximum volume ≥50 ml. The three bold lines represent one pregnancy that ended in miscarriage (Ab), the two that ended in preterm delivery (Prem); the gestational ages are shown in parenthesis.

The haematoma is probably formed by bleeding from the placental border. Since the placenta does not separate readily in the first and second trimester, the blood will track between the membranes and the uterine wall, but typically also elevates the border of the placenta. Most haematomata are located dependently, posteriorly, but if the placenta completely occupies the posterior uterine wall then the haematoma will be located laterally and anteriorly.

Because the blood never tracks beneath the placenta, there is no reason to expect that placental function will suffer and the average birth weight (3412 g, range 2600–4000) of the 20 babies born at term (average gestational age 275·0 days, range 253–299) supports this.

This study includes patients with vaginal bleeding at between 6 and 20 weeks and a haematoma of ≥50 ml. However, one other patient developed a haematoma after 20 weeks gestation. She had been seen several times between 18 and 20 weeks because of vaginal bleeding, but there was no evidence of haematoma. In week 22 she was readmitted with bleeding, when a 140 ml haematoma was observed and a live fetus; she miscarried the following day.

Other groups have investigated intrauterine haematomata, but they differ in their estimates of risk to the pregnancy. Jouppila (1985) reported one miscarriage but no preterm delivery in six women with haematomata having a mean diameter of ≥4 cm (≃32 ml). Similarly, Sauerbrei & Pham (1986) reported 13 women with haematomata >60 ml, of whom three had a miscarriage, five a preterm delivery and four a stillbirth. Nyberg *et al.* (1987) observed a rate of perinatal mortality of 1 in 10 in patients with subchorionic haematomata >60 ml and Abu-Yousef *et al.* (1987) found that nine of 10 patients with haematomata >45 ml had a miscarriage or preterm delivery. Three of these four series, all of which are smaller than ours, reported rates of miscarriage well above the reported rate of miscarriage (10–15%) after an episode of vaginal bleeding (Jouppila 1980; Mantoni 1985), whereas in the present study the rate of miscarriage was 4%. The apparent discrepancy may be explained in part by the small number of women and in part by the difference in the sample populations. The present study included an unselected group of patients from the region, whereas the other studies may very well have had an over-representation of high-risk pregnancies, as did our preliminary series. None of these authors reported the total number of women with threatened miscarriage, from which their patients were selected.

In an earlier phase of our study, the total observed occurrence of intrauterine echo-free lesions was 25% (Mantoni & Pedersen 1988). In the present study we found 23 women with haematomata ≥50 ml among 566 women with threatened miscarriage (4%). Among 233 patients admitted with vaginal bleeding between 12 and 20 weeks gestation 20 (9%) had haematomata ≥50 ml.

Large intrauterine haematomata are thus fairly common in patients with threatened miscarriage between 12 and 20 weeks gestation, but contrary to our original belief, they do not seem to involve any serious threat to the pregnancy. A patient in whom a haematoma is demonstrated may be reassured that the prognosis for her pregnancy is very good, but that she may expect additional bleeding.

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Effects of bilateral oophorectomy on lipoprotein metabolism

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Summary. The effects of surgical menopause on lipoprotein levels and their time course were studied in 31 premenopausal women who were undergoing hysterectomy and bilateral oophorectomy for non-malignant conditions. Lipoprotein levels were measured before oophorectomy and afterwards at 6 and 12 weeks, then at intervals of 3 months for 18 months. Low density lipoprotein (LDL) cholesterol levels rose significantly ($P<0{\cdot}05$) in the 6 weeks after operation from a mean of 3·57 (SD 0·66) mmol/l to 4·21 (SD 0·84) mmol/l with no significant changes thereafter. There were no significant changes in cholesterol in the other density fractions or in triglyceride levels. High density lipoprotein (HDL) subfractions were measured in 10 of the women to assess any change in the relative amounts of cholesterol carried on HDL2 and HDL3, since the protective effect of HDL is believed to be conferred by the HDL2 fraction only. No significant change was found in either fraction. The increase in LDL cholesterol would be expected to result in an appreciable increase in the risk of developing coronary heart disease, but cannot wholly account for the increase in cardiovascular disease associated with oophorectomy.

There is still controversy about whether the menopause increases the risk of coronary heart disease (CHD) (Heller & Jacobs 1978; Gordon *et al.* 1978). However, epidemiological evidence has pointed to an association between premature loss of ovarian function and elevated risk of cardiovascular disease (Bengtsson *et al.* 1973; Rosenberg *et al.* 1981).

Many studies have shown that serum cholesterol levels are significantly higher in postmenopausal women than in age-matched premenopausal women (Ritterband *et al* 1963; Aitken *et al.* 1971; Bengtsson *et al.* 1973; Kannel *et al.* 1976; Paterson *et al.* 1979; Notelovitz *et al.* 1983), although in two of the studies (Ritterband *et al* 1963; Aitken *et al* 1971) the difference was not apparent when only women of over 45 years of age were considered. Bengtsson *et al.* (1973) and Notelovitz *et al.* (1983) also found significantly higher triglyceride levels in postmenopausal women, while Aitken *et al.* (1971) and Paterson *et al.* (1979) did not. Results from the studies in which lipoprotein fractions were quantitated have been confusing (Ritterband *et al.* 1963; Kannel *et al.* 1976; Notelovitz *et al.* 1983), possibly due to the use of electrophoretic techniques which limited the investigators to the estimation of relative concentrations rather than

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absolute values. Two short-term longitudinal studies on the effects of bilateral oophorectomy on lipids have also produced contradictory results (Punnonen & Rauramo 1976, 1980; Pansini *et al.* 1984).

We have monitored lipoprotein levels prospectively in a group of healthy women before and for 18 months after oophorectomy to assess the effects on lipoprotein levels and to record the time course of these effects. In addition, we have measured high density lipoprotein (HDL) subclasses since it is believed that the protective effect of HDL lies in the HDL2 subfraction (Miller 1987).

Subjects and methods

Forty-two healthy premenopausal women undergoing hysterectomy and bilateral oophorectomy for non-malignant conditions were enrolled in the study. Premenopausal status was confirmed by serum oestradiol and gonadotrophin levels. Seven women did not return for follow-up and four withdrew from the study to be treated with oestrogen for vasomotor symptoms. The mean age of the 31 women who completed the study was 47 (SD 3·7) years and their mean body mass index was 25 (SD 3·5) kg/m^2. Eleven of the women smoked but did not alter their smoking habits for the duration of the trial. The women were not using hormone replacement therapy nor any drug liable to interfere with lipid metabolism during this study. Eleven of the women received a 3-month course of etidronate disodium, a potential new treatment for postmenopausal bone loss (Smith *et al.* 1989) between months 3 and 12 of the study period.

Blood for lipoprotein analysis was obtained after a 14-h fast before the operation and then postoperatively at 6 and 12 weeks and at intervals of 3 months thereafter for 18 months. The serum was separated within 3 h and stored at 4°C for a maximum of 5 days. Serum lipoproteins were separated into their density classes and quantitated as described previously (Farish *et al.* 1983). The between-batch coefficients of variation (CV) of the assay were VLDL = 11·7%, LDL = 2·5%, HDL = 4·2%. In addition, total HDL and HDL subfractions were quantified using the method of Eyre *et al.* (1981) in samples obtained from 10 of the women over the first 6 months of the study. The between-batch CV obtained were HDL2 = 10·0%, HDL3 = 5·3%

The results were analysed by a repeated measures analysis of variance using the Rummage statistics package (Bryce 1980). The analysis was rerun omitting the data collected from the 11 women who received etidronate therapy. Changes from pre-operation to 6 weeks after operation were also analysed using paired *t*-tests.

Results

Statistical analysis showed that etidronate disodium had no effect on lipoproteins. Therefore the results from the analysis including all the data are presented.

Lipoprotein levels pre-operatively and up to 18 months postoperatively are shown in Table 1. There were significant increases in both total and LDL cholesterol levels at 6 weeks after the operation and no significant changes thereafter. The mean increase in LDL cholesterol 18 months after operation was 19%. Only two of the 31 women failed to show any increase. There was no correlation between the pre-operative cholesterol level and the change after operation (r = 0·13, P>0·05). There were no changes in triglyceride, VLDL or HDL cholesterol levels

Table 2 shows levels of HDL and subfractions for 10 of the women. There were no significant changes in total HDL or either of the subfractions in this group for up to 6 months after operation.

Discussion

Previous longitudinal studies on the effects of bilateral oophorectomy on lipoproteins have produced conflicting results. Punnonen & Rauramo (1976) measured lipid levels in a group of women of average age 48 years before and at 1 and 7 months after bilateral oophorectomy. They found a transient rise in triglycerides with no change in serum cholesterol. In a later study (Punnonen & Rauramo 1980) they found that HDL cholesterol levels before and 1 month after oophorectomy did not differ significantly In a 3-month study Pansini *et al.* (1984) found significant rapid increases after oophorectomy in total cholesterol, HDL cholesterol and apolipoproteins A and B, with no change in triglycerides. Differences in the findings of these two groups of workers may be due to the small numbers of subjects studied

Our study demonstrates that surgical menopause causes a sharp rise in serum cholesterol,

Table 1. Serum lipoprotein values before and after oophorectomy in 31 women

Time of sampling	Total triglyceride (mmol/l)	Total cholesterol (mmol/l)	VLDL cholesterol (mmol/l)	LDL cholesterol (mmol/l)	HDL cholesterol (mmol/l)
Before operation	1·43 (0·67)	5·59 (0·81)	0·50 (0·25)	3·57 (0·66)	1·51 (0·35)
After operation					
6 weeks	1·56 (0·73)	6·27 (0·99)*	0·52 (0·26)	4·21 (0·84)*	1·52 (0·41)
3 months	1·36 (0·66)	6·10 (0·98)*	0·45 (0·25)	4·10 (0·95)*	1·56 (0·41)
6 months	1·28 (0·72)	5·98 (0·92)*	0·46 (0·40)	4·07 (0·75)*	1·51 (0·38)
9 months	1·31 (0·72)	6·12 (0·86)*	0·41 (0·32)	4·18 (0·74)*	1·59 (0·39)
12 months	1·30 (0·64)	6·13 (0·91)*	0·44 (0·33)	4·11 (0·73)*	1·51 (0·37)
15 months	1·35 (0·66)	6·22 (0·91)*	0·48 (0·34)	4·19 (0·73)*	1·53 (0·38)
18 months	1·36 (0·86)	6·29 (1·07)*	0·53 (0·39)	4·25 (0·90)*	1·56 (0·36)
Change pre-op, to 6 weeks post-op.	+0·13 (0·41)	+0·68 (0·54)†	+0·02 (0·20)	+0·64 (0·44)†	+0·01 (0·25)

Values are means (SD).
* Significantly different from pre-operative values ($P<0·05$)
† Significant change ($P<0·001$)

reflecting an increase in the LDL fraction. This occurs on average within 6 weeks of operation, with no further change during the next 18 months. No changes in VLDL cholesterol, total HDL cholesterol and subfractions or serum triglyceride levels are apparent for up to 18 months after the operation.

The time course of lipoprotein changes at the menopause has not been reported previously. The exact timing of a natural menopause is difficult to define, but by studying patients who have undergone surgical menopause this problem can be avoided. Our finding that lipoprotein levels are stable by 6 weeks after operation may be useful for workers studying the effects of hormone replacement therapy on lipoprotein levels, since the gathering of meaningful data depends on selecting subjects whose lipoprotein levels have reached a steady state post-menopause, particularly in the absence of a well-matched placebo group.

Several studies have indicated that premature menopause carries an increased risk of coronary heart disease (CHD) (Oliver & Boyd 1959; Sznajderman & Oliver 1963; Parrish *et al.* 1967). Results from two very large studies support this view. Follow-up with the Framingham Study over 24 years pointed to an increased risk of CHD associated with both natural and surgical menopause (Gordon *et al.* 1978). Comparisons in specified age groups up to age 55 showed a greater than twofold increase of cardiovascular disease in postmenopausal compared with premenopausal women. Similarly, analysis of data from the Nurses Health Study indicated that women who had undergone bilateral oophorectomy had more than twice the incidence of CHD compared with premenopausal women of the same age, although a natural menopause did not appear to affect risk (Colditz *et al.* 1987).

The relation between CHD and plasma cholesterol concentrations is well established (Gold-

Table 2. Cholesterol concentrations in total HDL and subfractions before and after oophorectomy in 10 women

Time of sampling	HDL cholesterol (mmol/l)	HDL2 cholesterol (mmol/l)	HDL3 cholesterol (mmol/l)
Before operation	1·51 (0·22)	0·41 (0·19)	1·04 (0·23)
After operation			
6 weeks	1·52 (0·27)	0·41 (0·17)	1·03 (0·15)
3 months	1·46 (0·24)	0·37 (0·12)	1·01 (0·15)
6 months	1·49 (0·17)	0·38 (0·11)	0·97 (0·07)

Values are means (SD).

stein *et al.* 1973; Lewis *et al.* 1974; Castelli *et al.* 1977). Several large clinical trials have reported that lowering cholesterol levels in high-risk individuals results in a decrease in risk. The Lipid Research Clinics Coronary Primary Prevention Trial (1984) estimated that a 1% reduction in serum cholesterol level conferred a 2% diminution in CHD risk, which is remarkably similar to the magnitude of the benefit predicted from epidemiological observations. In our study the mean increase in total cholesterol incurred at oophorectomy was 12·5%, which might be expected to increase the risk of CHD by 25%. There were no changes in any of the other lipoprotein risk markers measured.

In conclusion, our results suggest that surgical menopause alters lipoprotein levels sufficiently to cause an appreciable increase in the risk of developing CHD. However, these changes are not of sufficient magnitude to account for the reported increase in the occurrence of cardiovascular disease.

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Postpartum haemolytic uraemic syndrome precipitated by antibiotics. Case report

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Case report

A 21-year-old negroid woman booked for her third pregnancy at 28 weeks gestation. Pregnancy was uneventful until 38 weeks when she complained of a non-offensive vaginal discharge. A vaginal swab was taken, from which a β-haemolytic streptococcus was cultured. Six days later she was admitted in spontaneous labour and subsequently had an uncomplicated delivery of a 3 Kg infant. Within 24 h of delivery the patient became pyrexial with a temperature of 38°C. There were no adverse symptoms or physical signs to indicate a source of infection, but a repeat vaginal swab again showed β-haemolytic streptococcus. A course of ampicillin (500 mg four times daily) and metronidazole (400 mg three times daily) was given. The pyrexia settled within 24 h and she was discharged on the fourth day postpartum. Blood pressure on discharge was 120/70 mmHg.

Nine days after delivery she was admitted again complaining of colicky abdominal pain and bloody diarrhoea. On examination she was pyrexial (38 °C), with a pulse rate of 112/min and a blood pressure of 115/90 mmHg. There was no abdominal tenderness, but a profuse mucoid bloody diarrhoea was observed. Intravenous fluids and a course of intravenous metronidazole and cefuroxime were started. Initial haematological and biochemical indices were normal (Fig. 1) with a haemoglobin of 13.0 g/dl, white cell count of 12.8 × 10^9/l, serum creatinine of 60 and serum urea of 3.6 mmol/l. Blood cultures and cultures of stools grew no pathogens, and specific cultures for *Clostridium difficile* were negative. Sigmoidoscopy to 15 cm showed mucosal ulceration with pus. Biopsy showed mild non-specific inflammation not suggestive of ulcerative colitis or Crohn's disease.

On the second day after admission, the urine output was noticed to be poor (25 ml/h). Large amounts of fluid were being lost as a result of diarrhoea, and therefore intravenous fluids were increased. Subsequently, urine output improved to 65 ml/h, and remained at this level. However, there was a positive fluid balance of approximately 2 litres/24 h over the following 6 days, and biochemical evidence of progressive renal failure ensued. From their initial values, the serum creatinine and urea rose to 556 and 16.8 mmol/l respectively (Fig. 1). In addition, haemoglobin had fallen to 8.2 g/dl (white cell count 14.4 × 10^9/l, platelets 140 × 10^9/l) on day 7 of admission and to 6.8 g/dl (white cell count 16.78 × 10^9/l, platelets 100 × 10^9/l) by day 8. However, no abnormal or fragmented red cells were reported in the blood film, and the serum bilirubin remained within normal limits Her blood pressure had risen from 115/90 mmHg at the time of admission to 130/100 mmHg, and she remained pyrexial. A provisional diagnosis of haemolytic uraemic syndrome was made on day 7, and a course of vancomycin (125 mg four times daily) and nifedipine (5 mg three times daily) was commenced. Initially the profuse diarrhoea and colitis had resulted in dehydration and thus the diagnosis was not suspected until a marked fall in haemoglobin had occurred and renal function was rapidly deteriorating. Renal biopsy confirmed the diagnosis and treatment by dialysis and infusion of prostacyclin, fresh frozen plasma and cryoprecipitate commenced in a renal specialist unit. Satisfactory recovery of renal function occurred with this supportive therapy. Initial serum biochemistry suggested residual renal damage, but subsequent recovery appeared complete. A year after this event the

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serum creatinine and urea were within normal limits (creatinine 64 mmol/l, urea 4.5 mmol/l) and calculations based on the formula described by Hull *et al.* (1981) indicate a normal glomerular filtration rate. Although hypertensive and requiring medication when discharged, she is now normotensive (110/65 mmHg) without such treatment.

Discussion

Haemolytic uraemic syndrome is a condition characterized by acute renal failure, thrombocytopenia and microangiopathic haemolytic anaemia originally described as a fatal disease in children (Gasser *et al.*, 1955), but increasingly recognized in adults (O'Brien *et al.*, 1983). The association of the condition with pregnancy is an unusual, but well-described, event occurring typically in the postpartum period within a few days to approximately 10 weeks after an apparently normal pregnancy and delivery (Robson *et al.*, 1968; Wagoner *et al.*, 1968; Hayslett 1985). The condition has also been described in the first and second trimesters of pregnancy (Vandewalle *et al.*, 1975; Jacobs 1983), in association with ectopic pregnancy (Creasy & Morgan 1987), and in patients on the oral contraceptive pill (Schoolwerth *et al.*, 1976; Hoorntje *et al.*, 1981; Brown *et al.*, 1973; Stenger *et al.*, 1988). It has also been reported to occur in the postpartum period in animals (Roby *et al.*, 1987).

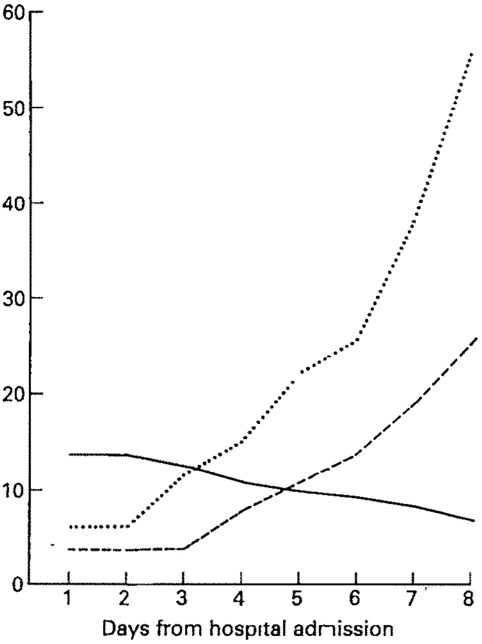

Fig. 1. Biochemical and haematological indices during the course of the disease. ———, Haemoglobin (g/dl); – – –, urea (mmol/l), ..., creatinine (μmol/l$\times 10^{-1}$)

The clinical presentation in many patients suggests that the haemolytic uraemic syndrome is consequent to an infectious process, and organisms associated with the syndrome are well described (Austin & Ray 1973; Davidson *et al.*, 1973, McKay & Wahle 1955; Rapaport *et al.*, 1964; Stenger *et al.*, 1988; Neill *et al.*, 1987; Carter *et al.*, 1987; Prober *et al.*, 1979; Chamovitz *et al.*, 1983; Baker *et al.*, 1974; Koster *et al.*, 1978). *Escherichia coli* 0157:H7, an organism that produced Shiga-like toxins (verocytotoxins), is the enteric pathogen most commonly isolated from patients with the syndrome (Karmali *et al.*, 1983, 1985a; Grandsen *et al.*, 1986; Taylor *et al.*, 1986; Kavi & Wise 1989). Current concepts of pathogenesis focus on the role of these toxins in systemic cellular injury that results in the microangiopathy and nephropathy of the haemolytic uraemic syndrome. Verocytotoxins have been shown to exhibit a direct and dose-dependent cytotoxic response on human vascular endothelial cells in culture, and have been proposed as the primary contributor to the development of the syndrome (Obrig *et al.*, 1987; Kavi *et al.*, 1987). Verocytotoxin causes platelet aggregation, thrombotic lesions and throbocytopenia as a result of release of endothelial cell factor VIII (Kavi *et al.*, 1987; Rose *et al.*, 1984), platelet aggregation independent of factor VIII (Rose *et al.*, 1985) and perhaps direct erythrocyte destruction (Lingwood *et al.* 1987). The association of the syndrome with pregnancy and patients taking combined oral contraception remains unexplained, but it may be an effect mediated by oestrogens. Oestrogens may facilitate the invasion of verocytotoxin across the mucosal barrier (Stenger *et al.*, 1988), this being the result of a reduced local immune response as shown by diminished antibody coating of bacteria in the urinary tract (Riedasch *et al.*, 1983).

There has been some concern that the antibiotic treatment of haemorrhagic colitis may increase the risk of the haemolylic uraemic syndrome (Carter *et al.*, 1987; Sack 1987; Tarr *et al.*, 1988). Two possible mechanisms to explain this occurrence have been proposed. Antimicrobial therapy may alter the bowel flora, thus allowing an overgrowth of verocytotoxin producing *E. coli* 0157:H7, allowing more toxin production, more absorption from the colon, or both. The resulting proliferation of this organism will be greater when the *E. coli* strain is resistant to the antibiotic given, while the sensitive, competing bowel flora is reduced (Sack 1987; Tarr *et al.*, 1988).

A second proposed mechanism by which antibiotics could increase the risk of the syndrome would be through lysis of, or sublethal damage to, the infecting *E. coli,* with a subsequent liberation of bacterial cytotoxins into the gut lumen (Tarr *et al.*, 1988). In support of this theory, increased extrabacterial cytotoxic activity has been demonstrated when polymyxin B (Karmali *et al* , 1985b) or trimethoprim-sulphamethoxazole (Karch *et al.*, 1986) is added to the growth medium of *E. coli in vitro.*

Antibiotics do not shorten the clinical course of haemorrhagic colitis or eradicate *E. coli* 0157:H7 carriage from stool (Riley *et al.*, 1983). Because of the potential risk of microangiopathic sequelae, it is thought that empirical use of antibiotics to treat haemorrhagic colitis due to *E. coli* 0157:H7 is unjustified. We consider that the acute onset of the syndrome in our patient was largely due to the overproduction of enteropathic *E. coli.* The hormonal millieu in addition to antibiotic therapy for the concommitant β-haemolytic streptococcus infection may have initiated this chain of events. Antibiotics are often used, somewhat indiscriminately, during pregnancy and the puerperium. This case demonstrates that the side-effects from antibiotics during this time can be life threatening. Though there was evidence of a β-haemolytic streptococcal infection, and antibiotic treatment was therefore justified, the development of the renal complications was insidious. Thus, it is important that this pattern of the clinical syndrome is recognized.

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CORRESPONDENCE

Maternal mortality in developing countries

Dear Sir,

In his commentary on maternal mortality in developing countries, Professor Harrison [*Br J Obstet Gynaecol* (1989) **96**, 1–3] mentioned that traditional birth attendants (TBAs) are part of 'a dangerous system of maternal health care' and spoke strangely and strongly against efforts of modern health workers to work with and have dialogue with us traditional medical practitioners. Perhaps you did not expect us to see and hear of your views but now that we have, we wanted to make a response since we do not think that they are fair or correct. We have never spoken against modern medicine and have seen and heard the good and powerful things it can perform.

We agree that some of our women may need your operations and medicines to save their lives due to the nature of their illnesses. Traditional medicine cannot cure all diseases but neither can modern medicine, and co-operation and understanding is always better than confrontation; what real harm has there been in the discussions between the TBAs and the modern health workers when the intentions have been sincere for the well-being of the women in need and the upliftment of the communities. They are trying their best. It is true we cannot do some of your operations but we know of many wonderful plants, roots and medicines and we pray to Almighty God to assist us in helping our people drive away their sicknesses.

It is strange that the Commentary forgot to mention the failure, mistakes, negligences and inhumane attitudes and practices of some modern doctors and hospitals. Does that make all modern medicine dangerous and useless? Many deaths are due to lack of experience, qualifications and ideology of some doctors and the way they keep us waiting and they try to treat our people; our young doctors have a lot to learn about being modern and not to forget their own people and be God fearing. We want water, electricity, roads and comforts but we do not necessarily have to have everything the same everywhere since we also have our own contributions to make. We have learnt that in some Western countries they are now relearning some of the healing methods and medicines of their forefathers and from other countries, using herbs, roots, acupuncture, and encouraging good habits and good foods to be healthy and drive away diseases.

We will continue to do our best, co-operate and work hand in hand with all people who are willing to work with us for peace, prosperity and well being of our people. If our TBAs cannot perform operations and the women cannot get to hospital in the middle of the night or in the rainy season then what are we to do, then we will pray and do whatever we can do. For some conditions our herbs and medicines are good and strong, for other conditions different medicines such as operations may be needed. Is it not better to work hand in hand together for progess and peace of all the people in the world, for everyone surely has something to offer however humble it may be.

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Dear Sir,

I read with interest the Commentary by Professor Harrison. I would like to congratulate him and associate myself with his views except on the building of maternity waiting homes at the hospital sites. This proposal is impractical and would not solve the problem of transportation of high-risk cases from remote villages to hospital.

First, the governments of developing countries cannot afford to build maternity waiting homes at the sites of their existing hospitals as these are still ill-equipped and inadequately staffed from lack of funds. Second, only a small fraction of the high-risk patients would use them—by far the majority of deliveries in developing countries still take place outside hospitals because of tenacity to old habits, inability to pay hospital bills and ignorance. Third, existing overburdened and financially handicapped hospital administrations would be unable to prevent such maternity waiting homes from becoming squalid slums.

The alternative to building maternity waiting homes at all hospital sites is decentralization of hospital management. The existing system of control of hospitals from headquarters, in terms of employment and deployment of staff—specialist and others—purchase and distribution of equipment, drugs and dressings and discipline has failed to bring medical care to the homes of rural dwellers who form the majority of the population. It is a colonial heritage that was probably justifiable in that era when a handful of qualified doctors and administrative staff had to meet the medical needs of vast areas. In its place should be the creation of autonomous regional or local government hospital boards, each with powers to employ and deploy its staff and control the funds it generates. This is the way to bring specialist services to local governments and rural dwellers.

This would automatically eliminate the undesirable traditional birth attendants (TBAs) who create more problems than they solve, and would make it unnecessary for nursing or paramedical staff to perform caesarean deliveries.

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Harrison K. A. (1989) Commentary. Maternal mortality in developing countries. *Br J Obstet Gynaecol* **96**, 1-3

Author's reply

Dear Sir,

An obvious merit in the contribution of the Sokoto Traditional Medical Practitioners' Association is in exposing the ills of the practice of orthodox medicine in an African setting. But its real worth is in showing once again what we, who want to work towards reducing the high maternal mortality rate in Africa, are up against.

His Royal Highness Dr Feyi-Waboso's reservations about maternity waiting homes are understandable but none is insurmountable. The cost of maternity waiting homes can be made to be affordable. In Malawi, for example, rural communities build their own and run them efficiently at little additional cost to the established health care services (B. Kwast, personal communications). In Cuba, vacant houses were simply taken over for the same purpose (Cardoso 1986). Early in this century, in France, Sweden and Finland, families who lived near maternity services gave accommodation to pregnant women from remote areas. Here in the Niger Delta area, the best of our traditional birth attendants used exactly the same principle in the decades before the acceptance of orthodox maternity care. We agree with His Royal Highness that maternity waiting homes can turn into slums through neglect. However, this is easily prevented by competent management as shown by the experience in the 1950s and 1960s at the ITUK MBANG Methodist Mission hospital in Nigeria (Dr E. Ritchie, personal communications).

No matter how well intentioned the establishment of maternity waiting homes is in improving access to good maternal health care before it is too late, one thing which cannot be achieved is its universal acceptance. The reasons are social and economic. Consequent on absence from home, there will be loss of earnings which some women cannot afford, and there will be separation from children which others will not tolerate. Serious objections will be raised in societies which traditionally seclude women of child-bearing age (Harrison 1989). Clearly the efficacy of maternity waiting homes awaits proper assessment through research.

Like His Royal Highness, we also believe that decentralization of hospital management is one way of achieving total population coverage with respect to maternity care. However, the main constraint is under-development. And there is no hope of overcoming permanently the consequences of under-development of which high maternal mortality is but one example, unless basic formal education is made universal, better still, compulsory. This is the real message traditional medical practitioners should help us to spread.

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Virilizing nodular ovarian stromal hyperthecosis, diabetes mellitus and insulin resistance in a postmenopausal woman

Dear Sir,
The report by Leedman *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 1095–1098] was stated to be the second case report of a virilizing nodular ovarian stromal hyperthecosis in a postmenopausal patient associated with diabetes mellitus, the first having been reported by Braithwaite *et al.* (1978). However, a further case was reported by van Heyningen *et al.* (1988).

The argument that the insulin resistance precedes the development of ovarian stromal hyperthecosis is difficult to refute, not because it is valid, but because it has not been investigated appropriately. This argument does, however, ignore that fact raised by van Heyningen *et al.* (1988) that the gonadotrophin levels were in the postmenopausal range in all three reported patients despite normal premenopausal oestradiol levels.

There must be some failure in the pituitary feedback mechanism which cannot be ascribed to insulin resistance. It seems that we are not able to say as yet which is the chicken and which is the egg in this condition.

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Needle aspiration of simple ovarian cysts in pregnancy. Case reports

Dear Sir,
Rodin *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 994–996] outline the advantages of transabdominal needle aspiration of simple ovarian cysts in pregnancy over the traditional practice of surgical excision. They cite the anaesthetic and thrombo-embolic risks of surgery for the mother, and quote a fetal loss rate as high as 25%.

Over 3 years in the Erinville Hospital, Cork, we have identified 23 simple unilocular ovarian cysts all with thin walls and no septa. All measured between 5 and 10 cm in diameter. These cysts were treated initially conservatively but nine required surgical excision because of pain. The remaining 14 were followed ultrasonically and all regressed spontaneously over the course of the following 8–10 weeks. None of these cysts caused any complication at delivery or subsequently. All patients were routinely scanned post-partum and no remaining cyst was identified. We agree with Rodin *et al.* that surgery is not necessary for uncomplicated, ultrasonically simple ovarian cysts in pregnancy. We further feel that in the absence of painful complications that such simple cysts can be safely dealt with without interference of any sort.

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Reference

Rodin A , Coltart T. M & Chapman M S (1989) Needle aspiration of simple ovarian cysts in pregnancy. *Br J Obstet Gynaecol* **96**, 994-996.

Measurement of cardiac output in pregnancy by thermodilution and impedance techniques

Dear Sir,

The article by Easterling *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 67–69] contains serious ambiguities and potential inaccuracies which I want to address.

The authors use only the values of cardiac output which, in the absence of the height and weight of each patient, is meaningless to judge the potential confidence of the reference method—thermodilution and to determine if the patient is hypodynamic, normodynamic or hyperdynamic.

The use of correlation coefficient to document an *agreement* between two inaccurate methods is completely incorrect (Bland & Altman 1986; Godfrey 1985). The use of correlation coefficient is legitimate only when one of the methods is a calibration standard. However, there is no gold standard for measurement of cardiac output. No method for measurement of cardiac output exhibits a better practical clinical accuracy than ± 20%; that includes thermodilution (Robin 1986). The reported correlation coefficient value, $r = 0.17$, thus represents a mathematically obtained number *unrelated to clinical agreement* between the two methods.

In addition to thermodilution's potential absolute inaccuracy when everything is done correctly, there is no mention of the method used for the thermodilution especially in respect to timing of the injectate with the respiratory cycle (Snyder *et al.* 1985; Verspille 1984). When the bolus of thermodilution medium is injected synchronously with the respiratory cycle, spontaneous or artificial, the reproducibility of the method improves but there can be up to an additional 35% increase in the inaccuracy of thermodilution's cardiac output value. *Reproducibility of thermodilution is not synonymous with its accuracy.*

The only correct way to compare the *agreement* between two inaccurate methods, such as thermodilution and bioimpedance, is to use a scattergram (Bland & Altman 1986; Godfrey 1985) and plot bands of accuracy of the reference method, i.e. ± 20% for thermodilution. If 75% of the scattergram points fall within the confidence band, the *agreement* between both methods is good.

When the procedure described above was performed for the study by Easterling *et al.* it could be concluded that (a) there was a systematic underestimation of bioimpedance in comparison to thermodilution by approximately 30%, and (b) 60% of the scattergram points fell within the ± 20% confidence band. The first point is conceivable when comparing two methods with a ± 20% inaccuracy of each. There can be a consistent disagreement up to 40% between two ± 20% inaccurate methods without violating the basic statistical principles. The 60% of the scattergram points within the confidence band shows an agreement, though not a good one.

The reason for using only 10 comparison points puts the authors in a direct conflict with known physiological facts. The authors are obviously convinced there is only one value of cardiac output for a patient. This was their justification for not being able to use the subsequently acquired cardiac output pairs for comparison. This is a fallacious assumption because cardiac output constantly changes in response to a varying oxygen demand and every new value of cardiac output and mean arterial pressure represents a new haemodynamic state. If the authors believe in a one-cardiac-output-value-per-patient theory, they should use at least 30 patients. With only 10 comparison pairs the study does not have sufficient statistical power.

The values of bioimpedance parameters listed in Table 1 point to a potential problem with the skin-to-electrode interface. In two patients, the $(dZ/dt)_{max}$ described incorrectly as dZ/dt, has a physically impossible value in relation to the base impedance, Z_0, listed as Total Fluid Index. This ratio $(dZ/dt)_{max}/Z_0$ is called the Index of Contractility (IC). As an index, it has a predictable normal range 0.033 0.065/Ohm. In the patient #6 and #8, the values of IC = 0.017/sec and 0.013/sec respectively have not been reported by any researcher or clinician.

One very important piece of information is missing from the study by Easterling *et al.* This involves a precise documentation of the instrumentation used, including the software revision number. This is valid both for the thermodilution computer and for NCCOM3. The manufacturer of the thermodilution computer is not listed and NCCOM3 (Noninvasive Continuous Cardiac Output Monitor) is listed as NCOOM3.

As far as the results are concerned, there is conflicting information published elsewhere. Two studies listed by Easterling *et al.* in Table 2 in comparing bioimpedance and thermodilution in pregnant women (Secher *et al.* 1979; Milsom *et al.* 1983) show good *r* values. D. I. Masaki *et* *al.* (USC, Los Angeles) presented a paper titled 'Noninvasive Measurement of Cardiac Output in Pregnancy by Thoracic Electrical Bioimpedance: Comparison with Thermodilution Method', at the 9th Annual Meeting of the Society of Prenatal Obstetricians (2/2/89) with completely opposite conclusions from Easterling *et al.* Masaki *et al.* report *good agreement* (more than 75% scattergram points within ± 20% of the confidence band) in 8 of 9 patients. They even report excellent correlation, $r = 0.91$, $P<0.001$.

In summary, we can conclude that the main contribution of Easterling *et al.* was in showing conclusively that judicious failure to assess critically the ambiguities and inaccuracies associated with thermodilution and utilization of incorrect methodology can be successfully used to support almost any conclusion.

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Author's reply

Dear Sir,

In our paper, 'Measurement of cardiac output in pregnancy by thermodilution and impedance techniques', we concluded that impedance technique cannot be used reliably in patients with severe pre-eclampsia. Mr Sramek contests these conclusions. His criticisms can be categorized under two broad topics: (i) statistical analysis and (ii) use of the equipment.

Mr Sramek is correct in his statement that correlation coefficient is a poor test to establish agreement between methods. However, the converse of that statement is not true. Correlation coefficient is an excellent method for demonstrating a lack of agreement between methods. The method of Bland and Altman (1986) referenced in the letter suggests that after comparing data with a scatter plot and correlation coefficient a more rigorous standard should be applied. A high degree of correlation can be achieved without necessarily achieving a high degree of agreement between methods. However, without a high degree of correlation further analysis is not necessary to confirm poor agreement.

To clarify, we have analysed our data by the method of Bland and Altman (1986). The mean difference between measurements is 3·3 l/min. The interval of the two standard deviations stretches from −0·63 l/min to 7·29 l/min. Given the lack of agreement and the well-established role of thermodilution in the measurement of cardiac output, one must challenge an assumption of the Bland-Altman method that each measure is equally likely to represent the true measure.

We used one data point from each patient when calculating our correlation coefficient. We did not do this because we were 'obviously convinced there is only one value of cardiac output for a patient'. Rather, the independence of data points is required by the assumptions of the statistical technique. Data points from the same patient are not independent and therefore cannot be used. A correlation coefficient can be inappropriately inflated by artifically increasing n and may be biased by including multiple measurements from subjects where the technique worked well. Interestingly, Mr Sramek cites two other studies in pregnancy where only correlation coefficient was used to establish agreement between methods. He seems to be interested in rigorous methodology only when the results do not agree with his interest in the equipment in question.

The great advantage of impedance technique over other methods of noninvasive measurement of cardiac output is the simplicity of use. We used the instrument as described in the instruction manual supplied by BoMed. This manual does not include the information regarding software revision that Mr Sramek requests. We used the 'long-term, silver-silver chloride electrodes' recommended for use with the equipment and supplied by BoMed. The skin was cleaned prior to application of the electrode. Mr Sramek suggests that a problem probably existed at the skin to electrode interface. This seems very unlikely. If this were the case, the TFI (the resistance from electrode to electrode across the skin and chest), would be increased. In the patients in question, the TFI was quite low suggesting good conductance throughout the entire system.

Mr Sramek makes several other peripheral points which should be addressed. First, we have demonstrated that cardiac output and body surface areas are not correlated in pregnancy (Easterling *et al.* 1986). Nevertheless, correction for body surface area will not affect agreement between methods since each measurement for an individual will be corrected by the same constant. Thermodilution technique was performed by widely accepted clinical methods where the contrast bolus is injected at end expiration. Since none of the patients was intubated, the effect of respiratory cycle is minimized. Mr Sramek quotes data presented as a poster by Masaki at the Society of Perinatal Obstetricians. Public comment on unpublished data is difficult. However, many patients in that study did not have severe pre-eclampsia. Some patients with severe pre-eclampsia had cardiac output measurements which were underestimated by impedance. These patients also had low maximum dZ/dt.

The accuracy of the impedance technique in normal pregnancy has been seriously challenged by de Swiet and Talbert (1986). Our data indicate that there is a more serious problem with the technique when applied to women with severe pre-eclampsia. The magnitude of the problem is evident without statistical analysis. As stated in the paper, we cannot comment on the accuracy of the method in pregnant patients without pre-eclampsia. The three normotensive patients in our study demonstrated a reasonable level of agreement. In the face of the existing data, we feel that it would be irresponsible to suggest that impedance measurement of cardiac output is accurate in pregnancies complicated by pre-eclampsia. Clinical use of the information could result in harm to the patient; use of the method for research would burden the literature with data that cannot be assumed to be accurate. We welcome further investigations into the use of the technique in pregnancy.

Finally, we find the failure of the methodology in the face of severe pre-eclampsia intriguing. A similar failure has been reported in case of hyperdynamic septic sepsis (Bernstein 1986). An understanding of the disruption in regional blood flow which complicates the use of impedance technique may provide important insight into the pathophysiology of each disease.

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BOOK REVIEWS

Complications of Gynecologic and Obstetric Management edited by Michael Newton & Edward Newton. W. B. Saunders Co., Philadelphia, London, 1988, 548 pages with figures and tables, £34.95

This book, a typically American multi-author production, is not without merit. Firstly, it demonstrates how far the American language and love of saying things as imprecisely as possible has moved away from the true English style. Sentences such as 'A good idea of the risk status of the patient and the procedures that may be necessary to optimise her pretreatment condition will then already have been developed' are repeated too often. Similarly, the need of any gynaecologist to go through a history and examination of all the systems of the body, even including a peep into the ears and nose, will amuse most working gynaecologists in the UK. I am all for thoroughness but such over-diligence in our practice would extend an average half-day National Health Service clinic to about 18 hours.

The chapters on complications of gynaecological and obstetric surgery are sound and comprehensive, although not enough emphasis is placed on how very rare the majority of these complications are. For example, in 28 years I have yet to see an acute thyrotoxic crisis following a gynaecological procedure but I suppose it must happen occasionally (they piquantly call it 'Thyroid storm'). The Americans' over-reliance on the use of antibiotics is obvious in this book Further, and I am not entirely xenophobic about the Americans, I do not understand how they can write a review on the complications of laparoscopy and not mention the RCOG British Study. The book is no longer up to date in that the problems of LASER surgery receive very limited discussion and cryo-surgery and hysteroscopy are only mentioned briefly.

In the obstetric section a little attention is given to the role of the controlled clinical trial in determining the management of breech delivery, but it appears that the authors regard large series of unselected breech vaginal deliveries as being just as relevant. Opinion rather than the results of clinical trials, conjecture and the notion of 'I have always done it this way' still regrettably pervade USA medicine. It is alarming that it is necessary to give so much space to the unnecessary operation of circumcision in the chapter on 'complications of operations and procedures for labour and delivery' and that this is the most common operation carried out in that country. Similarly, the caesarean section rate of around 20% is discussed without apology and little mention is given of how this appallingly high level might be reduced.

The chapter on radiotherapy is excellent and could be commended as a comprehensive treatise for MRCOG candidates. Similarly, the chapter on anaesthesia is very good indeed.

That a textbook of this type nowadays has to have a large chapter on 'legal complications' again emphasizes what dire straits both American and British medicine have now reached.

This is a good read for American practitioners but I can only recommend a few of the chapters to trainees in Britain. Most established practitioners would be better off updating their practice by simply reading the journals and attending the RCOG scientific meetings.

J. McGarry

Multimodal Treatment of Ovarian Cancer Volume 20, Monograph Series of the European Organisation for Research and Treatment of Cancer edited by Pier Franco Conte, Riccardo Rosso, Nicola Ragni & Jan B. Vermorken. Raven Press, New York, 1989, 351 pages with figures and tables, $111.50

This interesting book comprises the papers presented at a recent EORTC meeting on ovarian carcinoma. There are a large number of well-known contributors from Europe and North

America. However, more than anything else, this volume attests to the value of collaborative clinical research and illustrates the immense strides that have been made in this direction, particularly in Italy.

The book covers the full range of the oncology of ovarian cancer. It includes chapters on tumour biology and staging. There is a fascinating section on early ovarian cancer with two stimulating papers on limited surgery in both non-epithelial and epithelial ovarian cancer from the combined experience of three major departments of gynaecological oncology in Italy. Cytoreductive surgery and lymphadenectomy are discussed. A short session with three chapters is devoted to the diminishing role for radiotherapy in this disease. Two final sections address advanced ovarian cancer and new therapeutic modalities.

Among the many interesting chapters are those by P. F. Conte which include a discussion of the effects of ploidy and tumour cell kinetics. Dr Aapro write authoritatively about the current role for colony-forming assays. Dr Piver reviews several American studies on early ovarian cancer, pointing out how common borderline ovarian tumours are in early disease. The Italian experience suggests that there is a role for unilateral salpingo-oophorectomy in carefully selected patients with early stage ovarian cancer in order to preserve their fertility. Finally, the comparison of cisplatin and carboplatin in combination chemotherapy for advanced ovarian carcinoma illustrates yet again the inestimable value of collaborative effort.

For those interested in ovarian cancer this is an excellent source of material.

W. P. Soutter

Advances in Clinical Andrology edited by C. L. R. Barratt & I. D. Cooke. MTP Press Ltd, Lancaster, Boston, The Hague, Dordrecht, 1989, 118 pages with figures and tables, Dfl 94.00, US $47.00, UK £25.00

Andrology has never really come into its own as a speciality and remains a responsibility shared by interested urologists and gynaecologists. That having been said, there have been a number of important changes in approach over the last 10 years. A more critical appraisal of available treatment for male infertility has led to less empiricism and more frankness in dealing with patients, while a clearer understanding of the pathophysiology of spermatogenesis has indicated that simplistic remedies are unlikely to be forthcoming. At present, methods of coping with male infertility, such as donor insemination and IVF, are most successful where they bypass the problem rather than treat it.

This little book is a useful addition to the shelves. Put together following a meeting in 1986 at the Harris Birthright Research Centre in Sheffield, it is a readable exposition of the current state of the art. There are chapters on history and computing, including a synopsis of results from the large WHO study. T. D. Glover has written a thoughtful chapter on semen analysis. The place of surgery is fairly assessed by one of its leading proponents, W. F. Henry. There is a short chapter on varicocele which emphasizes the uncertain significance of this finding and the even greater uncertainty over treatment. Inevitably immunological aspects receive a good airing, one of the conclusions being a plea for a controlled prospective trial of cyclic prednisolone therapy. However, the likelihood of this being done seems to be small, mainly because of the side-effects. In the chapter on hormonal influences, I was surprised that mesterolone and tamoxifen were still presented as ways of improving fertility. Next there is a useful chapter on male accessory gland infection, and finally, an informative review from John Aitken and colleagues that points the way forward in research terms.

All in all this is a useful volume which should be read by those who are likely to encounter infertile men and women.

Allan Templeton

Contraception: Science and Practice by Marcus Filschie & John Guillebaud. Butterworths, London, 1989, 321 pages with figures and tables, £45.00

At the time when global population exceeds 5000 million and will certainly exceed 6000 million in the year 2000, the subject of contraception must be addressed. To this end the editors of *Contraception: Science and Practice* have assembled a group of experts in each field of birth control to give an overall view of the problem and explore the way forward.

The book is divided into 17 fully referenced chapters which cover all aspects of family planning and permanent sterilization, and is introduced by a very interesting demographic world review.

The sections on combined oral contraception include information on the metabolic effects of the pill and highlight areas that require further study and research. There is a very balanced account of adverse and beneficial effects of oral contraceptives, and the subject of cancer and the pill is discussed in detail.

Doctors working in the field will welcome the sensible advice given in the chapter on practical prescribing and will find the chapters reviewing the other reversible methods of birth control both informative and useful.

The section on abortion gives a comprehensive account which is both historical and practical, although there is nothing new to tell except that the problem has not gone away.

The account of female sterilization is mainly pictorial, but perhaps the estimated failure rate of 2 per 1000 is on the optimistic side.

There is little progress at present in the development of new male methods of contraception and more study is needed. Vasectomy would still appear to be the most reliable method of birth control with a quoted failure rate of 1 per 2000 and an 80% successful reversal rate.

This book gives an extensive review of the present situation, it is readable with a good format and deserves a place on the bookshelves of doctors working in the field of family planning.

Dorothy A. Tacchi

Fetal Monitoring. Physiology and Techniques of Antenatal and Intrapartum Assessment by John A. D. Spencer. Castle House Publications Ltd, Tunbridge Wells, 1989, 248 pages with figures and tables, £35.00

The contents of this book cover much more than electronic fetal monitoring. Indeed, they span the whole of the antenatal and intrapartum assessment in pregnancy. There are chapters on alpha-fetoprotein screening, antenatal diagnostic procedures, fetal movements, fetal breathing, the biophysical profile, Doppler ultrasound velocity waveforms and the biochemical evaluation of placental function. There are sections on screening for fetal growth retardation, modern techniques for monitoring the growth-retarded fetus and the compromised fetus in diabetic pregnancy, and a full discussion of fetal dangers in prolonged pregnancy. The interpretation of electronic fetal heart rate patterns can sometimes be difficult and there may be considerable dispute as to the significance of the fetal ECG waveform. Modern methods of computer analysis are assessed together with the biochemical diagnosis of fetal distress by pH and blood gas analysis. The indications for and the value of intrapartum monitoring is considered in detail and there is a section on the effect of analgesia on fetal heart rate patterns and the effects of intrapartum anoxia on long-term handicap. There is also a valuable and timely chapter on the medico-legal aspect of fetal monitoring. John Spencer has recruited specialists from the USA, the UK and mainland Europe to contribute to this comprehensive manual. Excellent editing, however, provides a uniformity of style which makes for easy reading. Some chapters are very short (41 chapters in 238 pages), but all have a comprehensive and up-to-date bibliography.

This is a book that all MRCOG candidates should read. Certainly all practising obstetricians will find at least some chapters valuable and balanced in assessing difficult and controversial clinical dilemmas. I think John Spencer is to be congratulated on an outstanding contribution to our understanding of pregnancy and birth.

B. V. Lewis

Baillière's Clinical Obstetrics and Gynaecology. International Practice and Research Volume 3/Number 1 March 1989. Operative Treatment of Ovarian Cancer edited by E. Burghardt & J. M. Monaghan. Baillière Tindall, London, Philadelphia, 1989, 215 pages with figures and tables, £18.50

This well-produced book is the result of a meeting held in Graz in 1988. The contributors are drawn from Europe, North America, China and Japan. It must be almost unique for a book to be devoted solely to the surgical management of ovarian cancer. This important topic is discussed lucidly and in an illuminating fashion by the many distinguished authors. The first section discusses the spread of ovarian carcinoma and its detection by laparotomy and by radioimmunoscintigraphy. The second section presents data on the techniques and results of cytoreductive surgery. The third section is devoted to lymphadenectomy and the information that has been derived from that. The fourth section consists of a discussion of the role of second-look surgery and of tumour markers.

The authors provide worthwhile and up-to-date information about the status of surgery in ovarian carcinoma. Dr Hacker addresses the controversial aspects of cytoreductive surgery, pointing out that aggressive surgical resection in patients with large metastatic tumours is unlikely to produce a cure but may confer more prolonged remission, especially when combined with platinum-based combination therapy. However, he ends his chapter with a plea for a prospective controlled study. Dr Webb, writing about his personal experience, showed that it was possible to produce optimal reduction in 75% of patients but that survival was worse if bowel resection was required. Dr Pfleiderer, in his chapter, pointed out the increasing proportion of cases of Stage III ovarian carcinoma diagnosed by histology only on the basis of biopsy of clinically normal omentum, lymph nodes or peritoneum. In his series such cases have increased from 3% in the mid 1970s to 16% in the mid 1980s. He wonders if some of the apparent improvement in survival for patients with Stage III disease may not be simply a reflection of the inclusion of these early cases. The interesting work performed in Graz by Professor Burghard and his colleagues, who have been exploring pelvic and para-aortic lymphadenectomy, is discussed in several separate chapters. Much valuable detail is provided which is worthy of careful digestion. His group also discuss the use of combinations of tumour markers in monitoring the progress of patients at the end of therapy.

This interesting book would be read with care by all interested in the management of ovarian cancer.

W. P. Soutter

The Physiology of Reproduction Volumes I and II edited by Ernst Knobil & Jimmy D. Neill. Raven Press, New York, 1988, 2633 pages with figures and tables, $362.50

This is an important publication. Knobil and Neill, themselves distinguished reproductive endocrinologists, have assembled a superb team of authors to produce a definitive reference work on reproductive physiology. The scope of the two volumes extends beyond that of endocrinology to include, for example, embryology and sexual differentiation. Each chapter includes a comprehensive set of references and clearly represents a major effort to produce a definitive review of the topic. There are sections on the development of reproductive systems, the hypothalamic pituitary gonadal axis in male and female, reproductive behaviour and its control, puberty and the endocrinology of pregnancy. The text is beautifully presented and well illustrated. Despite the price this should be an obligatory addition to medical libraries and to departments with a particular interest in reproductive medicine.

Stephen Franks

Books received some of which may be reviewed at a later date

Fetal and Neonatal Cardiology by Walter A. Long. W. B. Saunders Company, Philadelphia, London, 1990, 863 pages fully illustrated, £140

Dictionary of Abbreviations in Medical Sciences by Rolf Heister. Springer Verlag, Berlin, Heidelberg, London, 1989, 287 pages, DM 58.00

Perinatal and Multigeneration Carcinogenesis (IARC Scientific Publications No 96) edited by N. P. Napalkov, J. M. Rice, L. Tomatis & H. Yamasaki, Oxford University Press, Oxford, 1989, 436 pages with figures and tables, £48.00

Ovarian Pathology (Current Topics in Pathology, Vol 78 edited by Franciso Nogales. Springer-Verlag, Heidelberg, Berlin, 1989, 180 pages fully illustrated, DM 148.00

A Guide to Effective Care in Pregnancy and Childbirth by Murray Enkin, Marc J. N. C. Keirse & Iain Chalmers. Oxford University Press, Oxford, 1989, 376 pages, hardback £22.50, paperback £9.95

Viruses and Reproduction. A Bibliography compiled by Ernest L. Abel. Greenwood Press, London, 1988, 309 pages, £38.50

Proceedings and Symposiums

Fetal and Neonatal Physiological Measurements III (Proceedings of the Third International Conference on Fetal and Neonatal Physiological Measurements in Malmö/Ronneby, Sweden, 1988. Distributed by The Department of Obstetrics and Gynaecology, Malmo General Hospital, S-21401 Malmo Sweden, 1989. Edited by Gerhard Gennser, Karel Maršál, Nils Svenningsen & Kjell Lindström, 547 pages with figures and tables. No price given

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COMMENTARIES

Confidential enquiry into maternal death

The eleventh consecutive triennial report on maternal mortality was published by the Department of Health (1989). These reports were initiated in 1952; this one covers the triennium 1982–1984 and will be the last to refer to England and Wales alone. Future reports will include the whole of the United Kingdom. Such a milestone is but one manifestation of the flexibility and evolutionary nature of these reports.

In a special chapter of the latest report, Professor Sir Alexander Turnbull comprehensively reviews maternal mortality during the last century. In the early decades of this century, even with the introduction of antiseptic techniques, safe caesarean birth, the Midwives Act of 1902 and provision of antenatal care, maternal mortality rates remained very high at 4500 per million births. Such rates still prevail in much of Africa and Asia. The year 1937 saw the start of a sharp fall in mortality and since then the rate has approximately halved every 10 years.

The discovery of sulphonamides in 1937, and other antibiotics thereafter, was reflected by a dramatic fall in the contribution of sepsis to mortality. Better standards of education of women were important. However, the availability of skilled care was crucial. The use of blood transfusion, the introduction of ergometrine, an increasing number of births in hospital, better trained midwives and increasing skills amongst obstetricians promoted by the British, later to become the Royal College of Obstetricians and Gynaecologists founded in 1929, all contributed. A close association between the quality of obstetric care and falling maternal mortality was evident.

Between 1955 and 1984 the maternal mortality rate declined from 69·1 to 8·6 per 100 000 total births. The first six triennia were dominated by deaths from hypertensive disease of pregnancy, pulmonary embolism, haemorrhage and abortion. Abortion, often associated with criminal interference, was the main cause between 1958–60 and 1967–69. Implementation of the Abortion Act in 1968 was associated with a dramatic reduction in deaths involving criminal abortion in 1970–72 although the overall abortion death rate remained high. In 1973–75 deaths from legal abortion also decreased dramatically until in 1982–84 for the first time ever there were no deaths due to illegal abortion. The 11 direct deaths certified as due to abortion, four notably with spontaneous abortion, placed abortion fifth in the ranked table of direct deaths below hypertension, pulmonary embolism, anaesthesia, and amniotic fluid embolism.

Pulmonary embolism and hypertensive disease of pregnancy retain their position as the most frequent direct causes of maternal death with 25 cases attributed to each. Of the deaths due to pulmonary embolism, nine were antepartum, 12 followed caesarean birth and four followed normal delivery. A strong association was evident with maternal age greater than 35 years, obesity, restricted activity and operative delivery. Hypertension sometimes acts as a link between these factors. Bed rest is not recognized as a cure for any obstetric condition and should be prescribed with caution if at all. Women tending to spend time in bed, especially when obese, should be encouraged to perform regular leg exercises and mobilize when possible. Prophylactic anticoagulant therapy may be appropriate. When there is a history of thromboembolism or suggestive signs develop, detailed analysis should be made. When the diagnosis is entertained, a ventilation perfusion lung scan should be performed (de Swiet 1984). The hazards of investigation should be weighed against the risks of not treating pulmonary embolism. Anticoagulant therapy must be started early and administered effectively in confirmed cases.

Of the 25 deaths directly associated with hypertensive disease of pregnancy, 11 occurred with pre-eclampsia and 14 with eclampsia. In half of the eclamptic cases there was only one fit before death. The dominant finding at autopsy was cerebral haemorrhage, oedema or infarction. Failure to treat hypertension was a notable feature; obstetricians' interest in the diastolic blood pressure should not lead us to underestimate the threat of systolic hypertension to the maternal cerebrum. Failure to deliver expeditiously was also associated with therapeutic failure. Three deaths followed fluid overload in these patients who are usually vasoconstricted. In a further three patients excessive sedation led to death from respiratory arrest. Powerful sedative drugs are hazardous in high dosage, and serious consideration should be given to the use of magnesium sulphate as the anticonvulsant rather than diazepam or chlormethiazole. Magnesium does not lead to excessive maternal sedation (Gant & Worley 1980). Specialist consultation with a regional centre should be encouraged.

There were 18 deaths due directly to anaesthesia in 1982–84. This is a continuing decline in spite of the rising number of anaesthetics administered. Failure of intubation, regurgitation of stomach contents and deficient postoperative care were frequent. Liaison between anaesthetist and obstetrician must be improved with identification of high-risk patients. A superior level of anaesthetic expertise must be provided, bearing in mind the special risks of obstetric anaesthesia. A recent report by the Association of Anaesthetists (1987) highlights these problems.

Deaths from amniotic fluid embolism have increased in importance. It was only in 1961-63 that this group was recognized as a separate entity and now can only be included if proven histologically. There was only a small decline in the last two reports from 18 to 14 deaths. Basic understanding of the mechanism of expulsion of uterine contents is important. This is illustrated by a woman with pre-eclampsia who had an intrauterine death at 34 weeks gestation. Labour was induced by intravenous oxytocin followed by a prostaglandin pessary but because progress was slow, two more prostaglandin pessaries were inserted into the vagina. She continued to labour, dying unexpectedly 15 min after spontaneous rupture of the membranes, with an amniotic fluid embolism. The potent cumulative effect of exogenous and endogenous oxytocic stimuli was not appreciated. Although such a case shows substandard care, advances are awaited in the prevention and treatment of this difficult and dangerous condition.

The number of direct deaths due to haemorrhage has also fallen dramatically to nine deaths in 1982–84; four were antepartum, three postpartum and two were due to other obstetric trauma. It should be noted that haemorrhage contributed to 15 other deaths directly attributed to other causes. Two of the deaths were due to occult intra-abdominal bleeding and not to bleeding from the uterus, cervix or vagina. Anterior placenta praevia in the current pregnancy and previous caesarean section is associated with special risk. In a woman previously delivered by caesarean section in whom elective caesarean section is planned the placental site should be identified by ultrasound before operation. If the placenta is anterior and praevia, the increased risks are high enough to merit special preparations including cross-matching more blood than usual, alerting the anaesthetist and theatre staff, as well as informing the patient and her partner about possible hazards

There were only 10 direct deaths from ectopic pregnancy, the lowest number so far. During the same period, there has been a notable increase in the incidence of this condition. Increased awareness of the possible diagnosis, the use of ultrasound scanning, human chorionic gonadotrophin measurement, and diagnostic laparoscopy may all have contributed to this improvement. Earlier diagnosis is likely when conception is assisted; the role of transvaginal ultrasound is evolving and may make a significant contribution (Timor-Tritsch *et al.* 1989).

There were 69 deaths among women delivered by caesarean section during 1982–84. This was a decline from 87 deaths in the previous triennium in spite of a substantial rise in the number of caesarean sections performed. The fatality rate for all deaths following caesarean section has fallen to 0·37 per 1000 caesarean sections. When analysis is restricted to direct deaths within 42 days of emergency caesarean birth, the fatality rate was 0·36/1000, about four times the risk of vaginal birth. The death rate after elective section is 0·09/1000, about the same as after vaginal birth. Emergency caesarean is inherently more dangerous because of the lack of preparation and the stressed situation. The disadvantages of a rising caesarean section rate may be partially offset by more procedures being done electively, preferably with epidural anaesthesia.

The triennial reports of the confidential enquiry into maternal deaths have shown flexibility and have evolved in many ways. Consistency with WHO/FIGO definitions has been largely achieved. Late deaths, between 42 days and 1 year after delivery, are now recognized as such and will be excluded from future reports. The concept of direct, indirect and fortuitous deaths has been espoused. (Fortuitous deaths are excluded from WHO definitions of maternal death.) Since 1979–81 the term substandard care has been used instead of avoidable factors, taking into account not only failures in clinical care but other administrative and patient-related factors. Recent reports have proposed guidelines for the management of massive obstetric haemorrhage and suggested the establishment of regional teams with special expertise in the management of severe hypertensive disease of pregnancy. The persistence of substandard care in 1982–84 shows the continuing need for expert advice and clinical assistance to be readily available. This is not a restriction of clinical freedom but the guidance that is necessary when an obstetrician meets an uncommon but serious emergency. Consultant involvement in the labour ward must be encouraged.

The report is distributed free of charge to all obstetric and gynaecological consultants in England and Wales, relevant administrators and senior nursing officers. Ideally it should be circulated to all relevant junior staff for whom it is essential reading. Audit is a vital part of our activities: a point highlighted in the recent government review of the health service. Our speciality has reason to be proud of the reports of the Confidential Enquiry into Maternal Deaths; other disciplines are now following, citing the reports as examples of good practice. The report continues to evolve as is shown by the next one incorporating the whole of the United Kingdom. Particular attention needs to be directed to pulmonary embolism, amniotic fluid embolism, hypertensive disease and anaesthesia. Direct deaths have fallen more rapidly than indirect deaths and future reports must focus more closely on the latter.

The continued evolution of this report and the implementation of its recommendations should see maternal mortality continue to fall from 86 per million maternities in 1984 to 22 per million by the year 2000. Safety in childbirth must remain a primary aim of health care provision in any society.

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Timor-Tritsch I. E., Yeh M. N., Peisner D. B., Lesser K B. & Slavik T. A. (1989) The use of transvaginal ultrasonography in the diagnosis of ectopic pregnancy *Am J Obstet Gynecol* **161,** 157-161

Treatment of eclampsia

Eclampsia is the commonest cause of maternal mortality in England and Wales (DH 1989), despite the fact that it is a rare complication of pregnancy in these countries. Eclampsia occurs in only 0·036% of deliveries in Oxford and extrapolation of this figure gives an estimate of about 180 new cases a year in the United Kingdom (Redman 1988). In developing countries such as South Africa, eclampsia occurs much more frequently and is also the commonest cause of maternal death (Moodley *et al.* 1983). The fact that eclampsia is a rare complication of pregnancy in the United Kingdom results in obstetricians having little experience of this condition; consequently deficiencies in the management of eclampsia prevail. Despite the higher prevalence of eclampsia in developing countries and the wealth of experience gained in its management, maternal mortality rates remain high. This may be partly due to the fact that pre-eclampsia is a multisystem disease and the extent of involvement of the various organs is unpredictable.

Treatment of pre-eclampsia and eclampsia is also empirical because the aetiology of these conditions remains unknown. The most common cause of death is cerebral haemorrhage complicating acute hypertensive episodes (DH 1989). This has been supported by the demonstration of diffuse and focal areas of cerebral oedema by computerized tomography in non-fatal cases of eclampsia (Richards *et al.* 1986). The objectives in the management of eclampsia are the treatment and prevention of complications, and prompt delivery. Whilst the mode of delivery is not a contentious issue, conflicting opinions exist in the treatment of convulsions.

Historically, diminution of cortical irritability by sedation and isolation of the patient has been tried with little effect (Editorial 1976). Other forms of therapy, such as 8% chlormethiazole edisylate, diazepam infusions and 'lytic cocktail' containing promethazine hydrochloride, chlorpromazine and pethidine, have also been advocated. However, no clear benefit of one treatment over another with respect to maternal and infant mortality has been demonstrated.

Presently, the rational approach in the treatment of eclampsia is the use of a combination of an antihypertensive and an anticonvulsant drug. Most clinicians agree that diazepam should be used for the immediate control of convulsions as it is effective rapidly (Delgado-Escueta & Enrile-Bascal 1983). However, controversy exists in the choice of the most appropriate prophylactic anticonvulsant. Lean *et al.* (1968) demonstrated a mortality rate of only 3·3% in a population of eclamptic patients who were 'moribund' at the time of admission and were treated with an infusion of diazepam and the antihypertensive agent, dihydralazine. Concern over the respiratory and cortical depressant effects of large doses of diazepam on both fetus and mother have been expressed.

Magnesium sulphate is the anticonvulsant agent of choice for the treatment of eclampsia in the USA (Sibai *et al.* 1981; Pritchard 1982). The mechanism of action on the central nervous system is not known but it has been suggested that the cortical 'irritability' and agitation associated with severe pre-eclampsia and eclampsia are reduced (Pritchard 1982). The transient hypotensive effects may be mediated by a variety of mechanisms such as increased prostacyclin release from vascular endothelium, decreased angiotensin converting enzyme activity and inhibition of catecholamine release (Kaplan & Fisher 1988). Despite its generalized action, magnesium sulphate does not cross the blood–brain barrier and has no effect on the EEG abnormalities present with eclampsia (Kaplan & Fisher 1988). Furthermore, its use is still associated with a maternal mortality rate varying between 0·4 and 14·6% and convulsions persist in up to 10% of patients. Other treatment regimens may be as effective, as is demonstrated by a 75% decline in maternal mortality rate in the UK between 1956 and 1976 (Editorial 1976).

More recently phenytoin sodium has been advocated for the treatment of severe pre-eclampsia and eclampsia. Slater *et al.* (1987) have reported good results with this drug in patients with severe pre-eclampsia, but in our experience with eclampsia, the response to this anticonvulsant is highly variable. Properties of this drug which support its use include rapid crossing of the blood–brain barrier and a stabilizing effect on neuronal membranes.

In this issue of the journal, two reports address the question of the most appropriate anticonvulsant. Crowther (pp. 110–117) compared the efficacy of diazepam infusions with that of magnesium sulphate in a small group of patients with eclampsia and failed to demonstrate any major benefits of one regimen over the other. In the second study, Dommisse *et al.* (pp. 104–109) compared phenytoin therapy with that of magnesium sulphate in 22 patients with eclampsia. Phenytoin was not as effective in preventing recurrent convulsions; however, serum phenytoin levels were in the lower therapeutic range in the poor responders.

These and earlier reports highlight the need for large, randomized multicentre studies to establish the most appropriate anticonvulsant for the treatment of eclampsia. Such studies must be based on standardized protocols which take account of therapeutic drug levels, appropriate fluid therapy and correction of coagulation abnormalities In parallel with therapeutic studies, emphasis must be placed on preventive measures against the development of pre-eclampsia. The 'CLASP' (collaborative low dose aspirin) study being undertaken in the UK addresses this. This programme should be extended to developing countries where the prevalence of pre-eclampsia and eclampsia is considerably higher. Until convincing clinical research has been achieved, the management of eclampsia should involve the immediate control of convulsions with intravenous diazepam given by bolus injection, the judicious and prompt lowering of the raised blood pressure with dihydralazine, appropriate fluid therapy and early delivery. In addition, high priority should be given to the establishment of regional teams with special expertise to provide advice or take over management of patients with pre-eclampsia/eclampsia and there should be regular audits of all such cases.

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Erratum

Br J Obstet Gynaecol (1989) **96**, 1440–1444

Development of an invasive macroprolactinoma: a possible consequence of prolonged oestrogen replacement. Case report

J. S. BEVAN, J. SUSSMAN, A, ROBERTS, M. HOURIHAN, J. R. PETERS

Fig. 1. The publishers would like to apologise to the authors of this article for failing to include their corrections on the scatterproof of this figure. The individual frames needed to be relettered and repositioned. The correct version of the figure is now reproduced on the facing page.

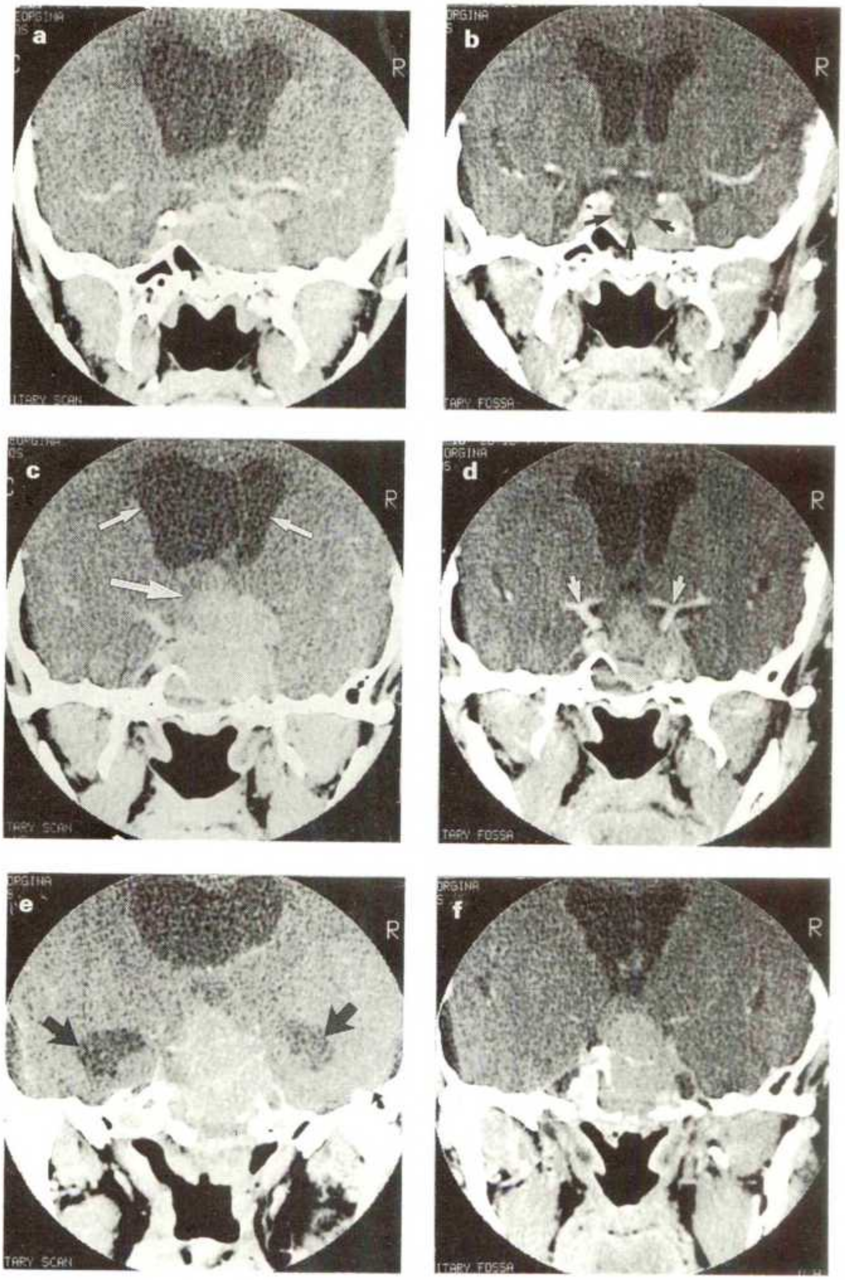

Fig. 1. Computerized tomography with contrast enhancement (Philips TX scanner). (a), (c) and (e) show coronal slices through anterior, middle and posterior regions of the tumour respectively, before, and (b), (d) and (f) after 8 weeks of bromocriptine. (b) Arrows indicate partial empty sella after bromocriptine. (c) Large arrow indicates upper part of suprasellar extension which has an inhomogeneous enhancement pattern. Small arrows indicate distended anterior horns of the lateral ventricles. (d) Internal carotid and middle cerebral arteries (arrows) clearly separate from tumour, and ventricular system less distended, after bromocriptine. (e) Arrows indicate distended inferior horns of the lateral ventricles, not visible after bromocriptine (f).

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Phenytoin sodium and magnesium sulphate in the management of eclampsia

J. DOMMISSE

Summary. Twenty-two patients with eclampsia were randomly allocated to receive either intravenous phenytoin sodium or intravenous magnesium sulphate. The groups were comparable. No side-effects occurred and therapeutic levels were obtained in both groups. While none of the 11 patients managed with magnesium sulphate had further convulsions, four of the 11 treated with phenytoin sodium did and were subsequently effectively treated with magnesium sulphate. These results suggest that phenytoin sodium is not as effective an anticonvulsant in eclampsia as is magnesium sulphate.

Magnesium sulphate is the anticonvulsant most widely used in the prevention and management of eclampsia in North America and many other parts of the world (Sibai *et al.* 1981; Pritchard *et al.* 1984). There is, however, considerable uncertainty about its mode of action and its safety, and its efficacy as an anticonvulsant drug has been seriously questioned (Donaldson 1986).

As eclampsia is primarily a convulsive state it would seem logical to use the most effective and widely used anticonvulsant drug available (Wilder *et al.* 1977; Gilman *et al.* 1985). Phenytoin sodium is well recognized as a specific drug for the prevention and control of epileptic seizures, and recent studies (Slater *et al.* 1987; Ryan *et al.* 1988) have advocated its use in the management of eclampsia and severe gestational proteinuric hypertension (pre-eclampsia). Phenytoin sodium was first used as an anticonvulsant in 1938, and its pharmacological action is well described (Gilman *et al.* 1985). It has a stabilizing effect on all neuronal membranes, and episodes of repetitive firing are especially suppressed (Wilder *et al.* 1977). Phenytoin enters the brain rapidly, and anticonvulsant activity is present as soon as 3 min after intravenous infusion (Wilder *et al.* 1977).

Although the mode of action of magnesium sulphate in preventing eclamptic seizures is not certain (Sibai *et al.* 1984) there can be no doubt as to its efficacy and its acceptance as standard treatment in most hospitals in the USA and many other parts of the world. Pritchard *et al.* (1984) describe 245 cases successfully treated with magnesium sulphate and state 'The cumulative results presented . . . provide a standard against which the results of treatment with new drugs and new treatment regimens can be compared'.

As we had limited experience in the use of intravenous phenytoin sodium in eclampsia, and no comparative studies have been published, a prospective study was undertaken to establish (i) whether recommended intravenous dosages of phenytoin sodium achieved therapeutic serum levels in pregnancy, (ii) the occurrence of serious side-effects, and (iii) the ability of intravenous phenytoin sodium to prevent further convulsions in patients with eclampsia compared to our standard magnesium sulphate regimen.

Patients and methods

The study was carried out in the Groote Schuur Hospital Maternity Centre which is the tertiary care referral hospital for an obstetric service that

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delivers 27 000 women annually, including 20–30 with eclampsia.

All patients with eclampsia, except those who had received previous anticonvulsant therapy, were included in the study which commenced on 1 January 1988 and was stopped after 11 months.

Patients were allocated to be treated with magnesium sulphate or phenytoin sodium according to a table of random numbers. The admitting doctor had no choice of regimen but was aware of the drug used, which was unavoidable in view of the serious potential risks with intravenously administered phenytoin sodium or magnesium sulphate.

Eleven patients received magnesium sulphate and 11 were managed with phenytoin sodium. One patient in the magnesium sulphate group had received phenobarbitone before admission and is included in the initial analysis but excluded from the comparative analysis. All the patients received clonazepam, 1–2 mg intravenously, before transfer to hospital or, if in hospital, immediately after the first convulsion.

Magnesium sulphate regimen

A 4 g loading dose in 200 ml saline was administered intravenously over 20–30 min, followed by a continuous infusion of 1 g/h (4 g in 200 ml saline in 4 h). In the last six patients this was increased to 2 g/h (8 g in 200 ml saline in 4 h). The infusion was continued for 24 h provided the tendon reflexes were present and the urine output was more than 30 ml/h.

Serum magnesium levels (Gindler & Heth 1971) were measured 30 min after the loading dose and every 6 h thereafter. The aim was to achieve 'therapeutic levels' between 1·25 and 2·5 mmol/l (2·5–5 meq/l). The occurrence of side-effects such as nausea, vomiting, absent tendon reflexes, respiratory depression, hypotension and arrhythmia was noted.

Phenytoin sodium regimen

The optimal intravenous dosage of phenytoin sodium in pregnancy is uncertain. Taylor *et al.* (1981) recommend a loading dose of 15 mg/kg body-weight. However, as it was not possible to weigh eclamptic patients we calculated an empirical dose of 500 mg which we increased to 1000 mg for the last five patients, based on average weights and the recommendations of Slater *et al.* (1987).

A small increase in dosage can cause a disproportionately large increase in phenytoin levels (Brodie & Feely 1988), and rapid administration may produce serious cardiac arrhythmias. The rate of direct intravenous injection should not exceed 50 mg/min (Taylor *et al.* 1981). Phenytoin may be diluted in normal saline and is stable for up to 7 h (Cunningham 1988).

The loading dose of phenytoin sodium was diluted in 200 ml saline and administered over not less than 20 min, ensuring an infusion rate of less than 50 mg/min. This was followed immediately by 500 mg diluted in 200 ml saline administered over the next 4 h. A final dose of 500 mg, administered over 4 h, was given 12 h after initiating therapy. Phenytoin serum levels were measured (Abbott TDX(R) Fluorescence polarization immunoassay) 30 min after the loading dose and every 6 h thereafter. The aim was to achieve therapeutic blood levels of 40–100 μmol/l (10–25 mg/l). The occurrence of side-effects such as nausea, vomiting, nystagmus, incoordination, dysarthia and arrhythmias was noted.

Management of hypertension

The blood pressure was assessed after completion of the loading dose of magnesium sulphate or phenytoin sodium. If the diastolic blood pressure (DBP) was ⩾ 115 mmHg, dihydralazine 25 mg in 200 ml normal saline was administered by controlled continuous intravenous infusion to achieve a gradual reduction of DBP to levels between 100 and 110 mmHg.

Obstetric management

Continuous cardiotocographic monitoring was employed. In all cases the pregnancy was terminated by induction or caesarean section once the convulsions and the hypertension were under control.

As eclampsia is a relatively rare occurrence it was initially planned to continue the study for 2 years, involving approximately 50 patients, unless untoward effects were encountered. The project was discontinued after 22 patients had entered the study as four of the 11 patients treated with phenytoin sodium had further convulsions.

Results

The clinical, haematological and biochemical

Table 1. Characteristics of the two treatment groups

	Magnesium sulphate (n = 11)			Phenytoin (n = 11)		
Characteristic	Range	Mean	(SD)	Range	Mean	(SD)
Age (years)	16–29	20·5	(4·4)	18–28	22·9	(4·36)
Gravidity	1–3	1·3	(0·67)	1–3	1·4	(0·68)
Gestation (weeks)	24–40	32·5	(5·31)	26–40	34·8	(4·23)
Number of fits	1–4	2	—	1–4	1·1	—
Blood pressure (mmHg)						
Systolic	120–220	171	(24·6)	140–220	168	(23·1)
Diastolic	80–140	114·5	(18·3)	90–140	115·4	(15·0)
Proteinuria 'Dipstix'	1–4	3	—	2–4	3	—

characteristics of the two groups appear in Tables 1 and 2. There were no significant differences. All the patients were antepartum and in each group two were in labour and nine not in labour. There was no fetal heart present in two patients in each group.

In the group treated with magnesium sulphate the serum magnesium levels were within the range of 1·25–2·5 mmol/l and there was no significant difference between the patients who received 1 g/h and those who received 2 g/h (Fig. 1).

The serum levels of phenytoin sodium are illustrated in Fig. 2. Most results were within the therapeutic range (40–100 µmol/l) (10–25 mg/l). The five patients who received 1000 mg as a loading dose had significantly higher levels than those receiving 500 mg.

No side-effects related to magnesium sulphate or phenytoin therapy were encountered in any of the patients.

None of the 11 patients managed with intravenous magnesium sulphate had further convulsions. One patient had received a dose of phenobarbitone before admission and was excluded in the final analysis. In comparison four patients in the phenytoin group had further convulsions despite therapeutic levels (Fig. 3) (P = 0·055, Fisher's exact test).

The first patient, a 19-year-old primigravida, was admitted after two eclamptic fits with a blood pressure of 160/110 mmHg and proteinuria 'three plus'. She had a convulsion 4 h after starting therapy with 500 mg phenytoin while receiving the second infusion. Serum phenytoin level was 45 µmol/l and the blood pressure was 170/110 mmHg. Magnesium sulphate was given and there were no further convulsions.

The second patient, a 28-year-old multiparous woman, was admitted after three convulsions. Blood pressure was 140/100 mmHg and proteinuria 'solid'. After receiving clonazepam, 1 mg intravenously, she received a loading dose of 1000 mg phenytoin intravenously over 30 min, followed by 500 mg infused over the next 4 h. The patient convulsed 2 h after starting therapy while receiving the second infusion. The blood pressure was 140/100 mmHg and the

Table 2. Comparison of haematological and biochemical results in the two treatment groups

	Magnesium sulphate group (n = 11)			Phenytoin sodium group (n = 11)		
	Range	Mean	(SD)	Range	Mean	(SD)
Haemoglobin (g/dl)	7·8–15·4	12·2	(2·64)	9·8–13·3	11·6	(1·31)
Platelets (10^3/mm^3)	67–494	220	(146)	26–300	187	(85)
Urea (mmol/l)	2·5–6·8	4·33	(1·59)	1·8–6·8	3·73	(1·44)
Creatinine (µmol/l)	53–97	78·2	(14·6)	62–106	87·9	(25·9)
Urate (mmol/l)	0·30–0·77	0·50	(0·14)	0·29–0·77	0·49	0·13
Protein (g/l)	44–67	53	(7·8)	48–61	54·4	4·1
Albumin (g/l)	22–35	27·5	(4·7)	26–36	35·4	10·4
Alkaline phosphatase (units/l)	124–279	201·3	(44·8)	127–366	238	118·5
Lactate dehydrogenase (units/l)	319–781	497	(183)	256–2877	756·6	927·4

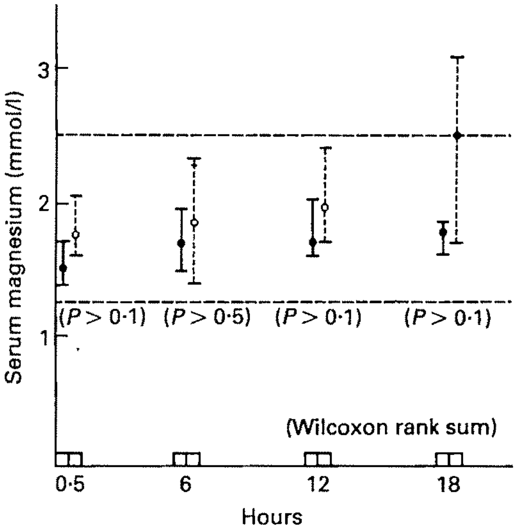

Fig. 1. Serum magnesium levels (mean and range) in 11 patients with eclampsia after treatment with intravenous magnesium sulphate at a rate of 1 g/h (|—•—|) (n = 5) or 2 g/h (|---○---|) (n = 6). The dashed horizontal lines indicate the therapeutic range 1·25–2·5 mmol/l.

serum phenytoin level was 65 µmol/l. Magnesium sulphate was given and no further convulsions occurred.

The third 'failure' was a 19-year-old primigravida admitted after two fits with a blood pressure of 190/130 mmHg and 'solid' proteinuria. She convulsed twice 2·5 h after receiving the loading dose of 1000 mg phenytoin. Her blood pressure was 130/90 mmHg and the serum phenytoin level was 70 µmol/l. Magnesium sulphate was administered and no further convulsions occurred.

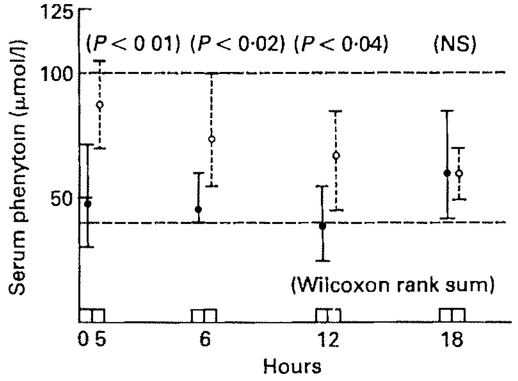

Fig. 2. Serum phenytoin levels (mean and range) in 11 patients with eclampsia after treatment with intravenous phenytoin sodium using a loading dose of 500 mg (|—•—|) (n = 6) or 1000 mg (|---○---|) (n = 5) The dashed horizontal lines indicate the therapeutic range 40–100 µmol/l.

The fourth patient, a 20-year-old primigravida, blood pressure 160/120 mmHg and 'solid' proteinuria, had one fit before admission and a second fit 12 h after starting treatment with a 1000 mg loading dose of phenytoin and 500 mg second dose. This was 5 h after delivery, her blood pressure was 130/90 mmHg and the third infusion (500 mg) had not yet been started. The phenytoin level was 46 µmol/l.

There were no maternal deaths. Eight patients in the magnesium sulphate group and seven in the phenytoin group were delivered by caesarean section and there were no neonatal deaths in either group. There were two stillbirths in each group but no fetal heart was present on admission of these four women.

There was a difference in the mean birthweight, which was 1672 g (range 400–2470) in the magnesium group and 2468 g (range 840–3880) in the phenytoin group ($P = 0·05$) despite no difference in the mean gestational ages.

Discussion

Magnesium sulphate may be administered either intravenously or intramuscularly. Dosage schemes vary, and Sibai *et al.* (1984) is of the opinion that the dose of magnesium sulphate should be increased above the 1–2 g/h usually advocated. However, magnesium is rapidly excreted, and provided the urine output is

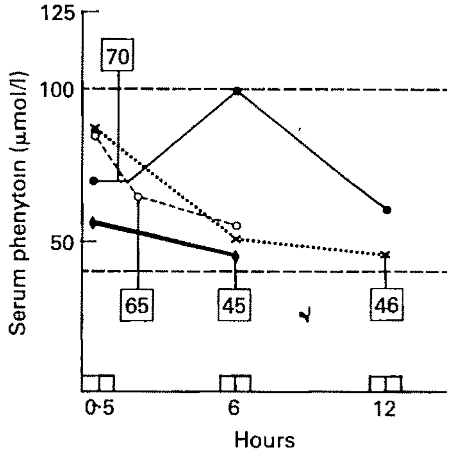

Fig. 3. Serum phenytoin levels in four eclamptic patients who had further convulsions despite treatment with phenytoin sodium □ = serum level at time of convulsion. The dashed horizontal lines indicate the therapeutic range 40–100 µmol/l

adequate most intravenous dosage schedules achieve a plateau between 1·25 and 2·25 mmol/l (2·5–5 meq/l) (Chesley 1979; Cruikshank *et al.* 1981). This is illustrated in this small series where increasing the dosage from 1 g to 2 g/h did not raise the serum levels significantly (Fig. 1). No patient had further convulsions on this dosage and at these levels in this study.

The dosage of intravenous phenytoin sodium in pregnancy is uncertain. We achieved therapeutic levels by increasing the loading dose empirically from 500 mg to 1000 mg (Fig. 2) and although no side-effects were reported these may have been masked by the clonazepam which all patients received. It is also difficult to diagnose cerebellar side-effects in seriously ill post-eclamptic patients.

Slater *et al.* (1987) varied the dosage according to body-weight, administering 750 mg (40–50 kg body-weight), 1000 mg (51–70 kg) or 1250 mg (> 70 kg) as a loading dose at up to 25 mg/min. An oral or intravenous dose was repeated 12 h later. At 30 min and 6 h after the infusion all 26 patients had levels within the range 28–80 µmol/l.

Ryan *et al.* (1988) used intravenous phenytoin in 45 patients employing four different regimens to evolve a dosage which ensured therapeutic levels with minimal side-effects. Their final recommendation, which was used in 28 patients, was to administer 10 mg/kg initially and 5 mg/kg 2 h later. Maintenance (oral) therapy was commenced after 12 h. This split regimen resulted in levels between 24 and 64 µmol/l. It is not possible to weigh eclamptic patients and therefore an estimated empirical dose is more practical.

Two of the patients who had further convulsions had phenytoin serum values in the low therapeutic range (45 and 46 µmol/l) although these would fall within the ranges accepted by Slater *et al.* (1987) (28–80 µmol/l) and Ryan *et al.* (1988) (24–64 µmol/l). The values in the other two patients were 65 and 70 µmol/l

While the statistical significance in this small series may be questioned, the results must also be judged against our experience and that of others as to the effectiveness of magnesium sulphate. Magnesium sulphate has been our standard regimen for the past 8 years and we have managed over 100 eclamptic patients with only three patients having recurrent convulsions after initiating therapy. In our opinion this study indicates that phenytoin sodium at therapeutic blood levels is not as effective as magnesium sulphate in the control of eclamptic convulsions.

The indication for anticonvulsant therapy in the management of severe gestational proteinuric hypertension (pre-eclampsia) as proposed by both Slater *et al.* (1987) and Ryan *et al.* (1988) is less certain, and Redman (1988) has stated that in most cases, control of the hypertension and termination of the pregnancy will resolve the condition. We are unaware of any random controlled study proving the efficacy of anticonvulsants in such cases. However, we would suggest that the use of phenytoin in severe pre-eclampsia is not justified if this drug failed to prevent further convulsions in four of 11 patients with eclampsia. Not only is magnesium sulphate a more effective anticonvulsant in eclampsia but there is some evidence of additional beneficial effects including enhancing the effects of vasodilatory antihypertensive drugs (Kelly *et al.* 1960; Cotton *et al.* 1984; Lee *et al.* 1984; James *et al.* 1988). This study supports the continued use of magnesium sulphate in eclampsia.

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I am indebted to the Department of Pharmacology, University of Cape Town, for the serum phenytoin estimations, to the obstetric laboratory, Groote Schuur Hospital Maternity Centre, for the serum magnesium levels, and to the obstetric registrars who cared so well for these patients.

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Magnesium sulphate versus diazepam in the management of eclampsia: a randomized controlled trial

CAROLINE CROWTHER

Summary. This randomized controlled trial compared the use of magnesium sulphate with diazepam as anticonvulsant in 51 eclamptic women. The use of magnesium sulphate was associated with less serious morbidity (in terms of recurrence of convulsions, cardiopulmonary problems, disseminated intravascular coagulopathy, and acute renal failure) but the difference was not statistically significant (relative risk 0·6; 95% CI 0·3 to 1·2). The one maternal death occurred in the magnesium sulphate group. Convulsions recurred in five (21%) women in the magnesium sulphate group and seven (26%) women in the diazepam group. Urine output poor enough to prompt diuretic stimulation was less frequent in the magnesium sulphate group than in the diazepam group (RR 0·3; 95% CI 0·1 to 0·9). Significantly fewer infants born in the magnesium sulphate group had low Apgar scores (<7 at 1 min) compared with those in the diazepam group (RR 0·6; 95% CI 0·4 to 0·9). There were two early neonatal deaths in the magnesium sulphate group, and three stillbirths in the diazepam group. This study suggests that magnesium sulphate has advantages over diazepam for the mother and the infant in the treatment of eclampsia, but the trial is small and should be replicated on a larger scale.

Eclampsia remains one of the leading causes of maternal and perinatal mortality in many parts of the world (Lopez-Llera *et al.* 1976; Porapakkham 1979; DHHS 1986; Moodley *et al.* 1983; Redman 1988). Present management of eclampsia aims to stop the convulsions and prevent recurrence, control the blood pressure, correct fluid and electrolyte imbalance and deliver the patient promptly. Anticonvulsant and antihypertensive drug therapy should protect the woman and her fetus from the deleterious effects of the convulsions, but should not expose either to additional risks from the therapy.

There is uncertainty as to the most effective anticonvulsant. Magnesium sulphate is favoured by some (Sibai *et al.* 1981; Moodley *et al.* 1983; Pritchard *et al.* 1984), and chlormethiazole (Darfour & Oduro 1972), diazepam (Lean *et al.* 1968; Ruoss 1974; Thakkar & Wacha 1978) and phenytoin (Moore & Redman 1987; Slater *et al.* 1987) by others. Excellent results have been reported for all these anticonvulsant drugs with respect to reducing maternal and perinatal mortality, but no direct comparison has ever been reported. In the UK, diazepam, chlormethiazole and phenytoin are favoured (Wightman *et al.* 1978; Slater *et al.* 1987), whereas magnesium sulphate is the drug most widely used in the USA (Pritchard *et al.* 1984).

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the anticonvulsant diazepam has been used to manage eclampsia. It is inexpensive, readily available, easily administered and, therefore, suitable for use by staff in outlying clinics and hospitals before the eclamptic woman can be transferred to the Harare Maternity Hospital. However, a retrospective study of eclampsia in Harare revealed high rates of maternal (9%) and perinatal (29%) mortality when diazepam was used to manage eclamptic patients (Crowther 1985*a*).

The disadvantage of diazepam is that heavy prolonged sedation of the woman increases the risk of aspiration pneumonia and other respiratory problems which contribute to maternal mortality and morbidity (Crowther 1986; Slater *et al.* 1987). Large doses of diazepam are often required and these can lead to neonatal respiratory depression, hypothermia, hypotonia, and poor sucking (McCarthy *et al.* 1973; Cree *et al.* 1973).

Magnesium sulphate, whilst free of the risks of heavy sedation (Pritchard & Pritchard 1975; Moodley *et al.* 1983), has been associated with cardiorespiratory arrest (McCubbin & Sibai 1981; Pritchard *et al.* 1984; Richards *et al.* 1985) and, when given intravenously, with neonatal hypermagnesaemia (Lipsitz 1971).

This is a report of a randomized trial comparing magnesium sulphate with diazepam. The study objectives were to compare the two drugs in respect of recurrence of convulsions, cardiopulmonary and renal function, and perinatal outcome. The study was conducted at Harare Maternity Hospital, Zimbabwe. The main comparison was between the use of the two drugs in women in, or transferred to, the hospital with eclampsia. Secondary analyses compared the two drug regimens in women who had received no previous anticonvulsant treatment and in women who had received diazepam in outlying clinics or hospitals before being transferred to Harare Maternity Hospital.

Patients and methods

Harare Maternity Hospital is a referral centre for high-risk obstetric patients. Of the 34 women with eclampsia treated at the hospital in 1982, 25 (74%) were referred from the municipal maternity clinics in the residential suburbs, which are staffed by sister midwives and medical assistants (Crowther 1985*b*). These clinics provide care for pregnant women judged to be at low risk. In addition, Harare Maternity Hospital receives high-risk referrals, which include eclamptic patients, from clinics and hospitals throughout the country.

Women presenting to Harare Maternity Hospital with antepartum eclampsia between 1 January 1984 and 30 April 1986 were considered for entry into the study regardless of any previous anticonvulsant therapy received. Women were excluded if the gestational age was less than 28 weeks, if they had already been delivered or if the fetus was dead upon admission. Approval for the study was given by the University Research Board, and this approval did not require any formal consent to be sought from the extremely ill women who were eligible to participate in the study.

At entry, women were randomly allocated to either magnesium sulphate therapy or diazepam therapy by opening the next of a set of consecutively numbered, sealed, opaque envelopes; 1:1 randomization was organized in blocks of six with no prognostic stratification. These envelopes were prepared by the author who was not involved in patient enrolment. Serious maternal morbidity after eclampsia was defined as one or a combination of the following: recurrence of convulsions, cardiopulmonary problems, disseminated intravascular coagulopathy, and acute renal failure. The frequency of such morbidity associated with diazepam was estimated to be 52% from previous observational studies (Crowther 1985*a* and unpublished observations). The intention was to maximize the sample size within the time available; the final trial size was 51. A trial of this size would have a 50% chance (beta error 0·50) of detecting a statistically significant difference at the 5% level (alpha error 0·05) if the rate of maternal morbidity were reduced by half by the use of magnesium sulphate.

Management

Investigations requested on all women at entry included full blood count, platelets, urea and electrolytes, serum creatinine, uric acid, fibrinogen and fibrin degradation products. All patients were closely monitored with frequent pulse and blood pressure recordings and hourly assessment of respiratory rate, conscious level and urine output. All the women had a urinary catheter; a central venous pressure line was inserted if this was considered appropriate.

Fluids were given intravenously to maintain an adequate urine output. Dihydralazine, 12·5 mg, was given intravenously, as necessary, to maintain diastolic blood pressure below 110 mmHg.

Vaginal delivery was planned if delivery was considered likely within 8 h. All other patients were delivered immediately by caesarean section as were those with failure to progress in labour or if fetal distress developed.

Drug regimens

Magnesium sulphate therapy. Magnesium sulphate was administered as described by Pritchard & Pritchard (1975). Magnesium sulphate, 4 g (8 ml of 50% magnesium sulphate solution diluted with 12 ml sterile water), was given intravenously slowly over 3–5 min to stop the convulsions. This was followed by 10 g of magnesium sulphate given intramuscularly (10 ml of 50% magnesium sulphate solution into each buttock), to prevent recurrence of convulsions. If convulsions recurred, a further 2 g magnesium sulphate was given intravenously over 3 min. A further 5 g of magnesium sulphate was given intramuscularly every 4 h (using alternate buttocks) for the first 24 h after delivery provided that, on assessment by the medical staff, the respiratory rate was >16/min, the urine output was >25 ml/h and knee jerks were present.

Diazepam therapy. Diazepam, 10 mg, was given intravenously to terminate the convulsions, and repeated if convulsions recurred. This was followed by an intravenous infusion of diazepam, 80 mg in 1 litre of 5% dextrose. The speed of the infusion was varied with the aim of overcoming restlessness and keeping the patient sedated. The 80 mg/l diazepam drip was continued for 24 h after delivery, and followed by a 40 mg/l diazepam drip for a further 24 h.

Statistical analysis

The χ^2-test was used to compare frequencies between groups, and Student's *t*-test to compare means between groups. Confidence intervals of the relative risks were derived using the method recommended by Katz *et al.* (1978). There were no interim analyses.

Results

Of the 51 women in the study, 24 were allocated to receive magnesium sulphate and 27 to receive diazepam. The two groups were comparable for important characteristics (Table 1). There were six twin pregnancies, three in each study group. Before enrolment to the study, 17 (71%) women in the magnesium sulphate group and 17 (63%) women in the diazepam group had already received emergency anticonvulsant therapy with diazepam. No patient had received magnesium sulphate. There were no statistically significant differences in gestation between the two groups.

Maternal outcome

No problems of buttock abscesses with intramuscular magnesium sulphate injection were seen. Maternal outcome is summarized in Table 2. Most women were delivered by caesarean section, 19 (79%) in the magnesium sulphate group and 18 (67%) in the diazepam group. Maternal morbidity, in terms of recurrence of convulsions, cardiopulmonary problems, disseminated intravascular coagulopathy, and acute renal failure, occurred in seven (29%) women in the magne-

Table 1. Characteristics of women in magnesium sulphate and diazepam treatment groups

	MgSO$_4$ (n=24)		Diazepam (n=27)	
Maternal age (years)	21·3	(4·9)	21·3	(5·4)
Parity				
0	17	(71)	17	(63)
1–3	4	(17)	6	(22)
>3	3	(12)	4	(15)
Previous diazepam therapy	17	(71)	17	(63)
No antenatal care	9	(38)	11	(41)
Transfer to hospital	8	(33)	7	(26)
Median time from first fit to entry (h) (range)	1·0	(0–16)	1·5	(0–12)
Mean arterial pressure at entry (mmHg)	130·4	(18·1)	125·4	(14·0)
Proteinuria at entry (Albustix)				
1+	6	(25)	5	(19)
2+	8	(33)	9	(33)
⩾3+	10	(42)	13	(48)
Gestation at delivery (weeks)				
<34	6	(25)	3	(11)
24–36	6	(25)	10	(37)
37+	12	(50)	14	(52)
Birthweight (g)	2323	(663)	2384	(507)

Results are mean (SD) or *n* (%) as appropriate.

Table 2. Comparison of maternal complications in the two treatment groups

	$MgSO_4$ (n=24)	Diazepam (n=27)	Relative risk	95% CI
Maternal morbidity*	7 (29)	14 (52)	0·6	0·3 to 1·2
Recurrence of convulsions	5 (21)	7 (26)	0·8	0·3 to 2·2
Pneumonia	0	3		
Respiratory depression	0	1		
Cardiac arrest	1	0		
Coagulopathy	1	2		
Acute renal failure	0	1		
Recurrence of convulsion after 1 h of therapy	1 (4)	4 (15)	0·3	0·3 to 2·4
Diminished urine output	3	12	0·3	0·1 to 0·9
Urine output < 500 ml 12 h after delivery	1	6	0·2	0·02 to 1·5
Maternal death	1	0		

Results are n (%).
*Recurrence of convulsions, cardiorespiratory problems, disseminated intravascular coagulopathy and acute renal failure.

sium sulphate group and in 14 (52%) women in the diazepam group (RR 0·6; 95% CI 0·3 to 1·2).

Most of the recurrent convulsions occurred within the first hour after entry and initial drug therapy (four in the magnesium group and three in the diazepam group). Convulsions after the first hour of stabilization occurred in one (4%) woman in the magnesium sulphate group, 7·5 h after commencing treatment. Erroneously, this woman had not received maintenance doses of magnesium sulphate therapy specified in the study protocol. In the diazepam group, four (15%) women had a further convulsion after the first hour of stabilization (at 1·5, 2·5, 3·5 and 7·5 h after entry).

No women in the magnesium sulphate group developed pneumonia, but three women in the diazepam group did. In two this was considered to be related to heavy sedation and immobilization, and in the third it followed aspiration of vomit. This woman required ventilation in the intensive care unit. One woman in the diazepam group required ventilation for respiratory depression secondary to sedation. A cardiac arrest occurred in one woman immediately after the initial 4 g intravenous loading injection of magnesium sulphate, probably as a result of too rapid an injection. Resuscitation was successful and the woman and the infant survived.

Disseminated intravascular coagulopathy developed in one woman in the magnesium sulphate group, and in two women in the diazepam group.

One woman in the diazepam group developed acute renal failure and required haemodialysis for 5 days. She made a full recovery. Urine output was considered sufficiently diminished to warrant diuretic stimulation in three women in the magnesium sulphate group, and in 12 women in the diazepam group (RR 0·3; CI 0·1 to 0·9). In the magnesium sulphate group one (4%) woman had a urine output of < 500 ml in the first 12 h after delivery compared with six (22%) women in the diazepam group.

There was one maternal death, a 20-year-old primigravida in the magnesium sulphate group who had received no antenatal care. She had a convulsion at home and was transferred with a diazepam drip from a peripheral hospital after an initial 10 mg dose of diazepam had been given intravenously to terminate the convulsions. During transfer she had a cardiorespiratory arrest and was resuscitated. She was unconscious on admission at time of entry into the trial and required ventilation. At caesarean section an infant weighing 1820 g was born with Apgar scores of 1 and 3 at 1 and 5 min respectively. The woman never regained consciousness. She was certified brain dead 3 days after admission. Death was considered to be due to severe hypoxia secondary to cardiorespiratory arrest either during an eclamptic seizure or as a consequence of treatment with diazepam.

Fetal outcome

Fetal outcome is summarized in Table 3. With the twin pregnancies there were 27 infants in the magnesium sulphate group and 30 infants in the diazepam group. Significantly fewer infants (12,

Table 3. Comparison of infant outcome in the two groups

	$MgSO_4$ (n=27)	Diazepam (n=30)	Relative risk	95% CI
Apgar score				
<7 at 1 min	12 (44)	24 (80)	0·6	0·4 to 0·9
<7 at 5 min	6 (22)	14 (47)	0·5	0·2 to 1·1
Stillbirth	0	3		
Livebirth	27	27		
Early neonatal death	2	0		
Intubated	4 (15)	10 (33)	0·4	0·2 to 1·3
Admitted to neonatal intensive care unit	17 (63)	22 (82)	0·9	0·6 to 1·2
Days on neonatal unit Median (range)	2 (0–42)	5 (0–34)		
Length of stay >7 days	4	7	0·6	0·2 to 1·9

Results are *n* (%).

44%) born in the magnesium sulphate group had low Apgar scores (≤7 at 1 min) compared with those in the diazepam group (24, 80%) (RR 0·6; 95% CI 0·4 to 0·9). This difference persisted at 5 min (RR 0·5; 95% CI 0·2 to 1·1). Fewer infants in the magnesium sulphate group required intubation and intermittent positive pressure ventilation at delivery or admission to the neonatal intensive care unit compared with those in the diazepam group, although these differences were not statistically significant. The median length of stay in the neonatal unit was 2 days (range 0–42) for infants in the magnesium sulphate group and 5 days (range 0–34) for infants in the diazepam group. Four (15%) infants in the magnesium sulphate group required admission to the neonatal care unit for >7 days compared with seven (23%)infants in the diazepam group.

There were two perinatal deaths in the magnesium sulphate group. Both babies were born by caesarean section with birthweights of 1000 g and 1610 g and died from severe hyaline membrane disease within 2 days of birth. There were three perinatal deaths in the diazepam group, all stillbirths. Two were fresh stillbirths with birthweights of 2150 g and 2750 g; the fetal heart was 'lost' during labour and both were born vaginally. The third death was of a second twin weighing 1600 g which showed signs of early maceration at delivery.

Secondary analyses

Maternal and fetal outcomes were reviewed for women who received no previous anticonvulsant treatment before entry into the study (Tables 4 and 5). In both treatment groups maternal morbidity was higher than in those who had already had anticonvulsant therapy. This was mainly mediated by an increase in the recurrence of convulsions, but maternal morbidity was still higher in the diazepam group. Recurrence of convulsions accounted for all the maternal morbidity observed in the magnesium sulphate group. Beneficial effects were observed on fetal outcome with magnesium sulphate in that significantly fewer infants had Apgar scores of <7 at 1 min compared with the diazepam group (RR 0·4; 95% CI 0·2 to 1·0) (Table 5).

Discussion

There is no consensus about the choice of anticonvulsant for the management of eclampsia. Formal assessment of alternative agents in randomized controlled trials is difficult because of the nature of the condition and its infrequent occurrence. The present study suggests that magnesium sulphate may be superior to diazepam as an anticonvulsant in patients with eclampsia. Overall there was less serious maternal morbidity when magnesium sulphate was used, but this difference was not statistically significant (RR 0·6; 95% CI 0·3 to 1·2). Convulsions recurred in both study groups, although less frequently with magnesium sulphate. Only one (4%) woman in the magnesium sulphate group had a convulsion after the stabilization period of 1 h and this was probably due to nonadherence to management guidelines. The 21% overall recurrence rate of convulsions with magnesium sulphate was higher than the 12% recurrence rate reported by Pritchard *et al.* (1984). Of the five women in the magnesium sulphate group who had recurrence of convulsions, these occurred in four women within the first hour of

Table 4. Comparison of maternal complications between the treatment groups in women not given diazepam before study entry

	$MgSO_4$ (n=7)	Diazepam (n=10)	Relative risk	95% CI
Maternal morbidity	4 (57)	7 (70)	0·8	0·4 to 1·7
Recurrence of convulsions	4 (57)	4 (40)	1·4	0·5 to 3·9
Pneumonia	0	2		
Respiratory depression	0	0		
Cardiac arrest	0	0		
Coagulopathy	0	1		
Acute renal failure	0	0		
Recurrence of convulsion after 1 h of therapy	1 (14)	2 (20)	0·7	0·1 to 6·4
Diminished urine output	1	2	0·7	0·1 to 6·4
Urine output < 500 ml 12 h after delivery	0	0		
Maternal death	0	0		

Results are n (%).

starting treatment and responded to a 2 g intravenous bolus of magnesium sulphate. Peak serum levels of magnesium occur 1 h after intramuscular injection (Chesley 1979) after which, with adherence to the protocol, recurrence should be rare.

In contrast, four (15%) women who received diazepam had a recurrence of a convulsion 1 h or more after 'loading doses', and at a time when stabilization should have been achieved. The risk of maternal and perinatal death increases as the number of fits increases (Lopez-Llera *et al.* 1976; Moodley *et al.* 1983), and effective treatment should prevent further convulsions. The recurrence rate of 26% after diazepam treatment is considerably higher than the rate of 2% reported by Lean *et al.* (1968), and the 7% recurrence rate reported by Thakkar & Wacha (1978), and this may mean that, in our study, diazepam serum levels were inadequate. Intravenous titration of drugs requires extra nursing vigilance which is not always possible in a busy maternity unit in the developing world. Too little diazepam results in recurrence of convulsions, too much diazepam results in over-sedation and respiratory depression. In such circumstances the most appropriate route of administration may be intramuscular because when a drug is given intramuscularly there is less need for such close monitoring. Great care still needs to be exercised, however, so that correct drug dosages are given in the appropriate manner and to ensure that the follow-up protocol is adhered to (Pritchard *et al.* 1984).

The respiratory problems secondary to heavy prolonged sedation with diazepam seen in the present study have been reported previously (Moodley *et al.* 1983), but they were not a prob-

Table 5. Comparison of infant outcome between the treatment groups in women not given diazepam before study entry

	$MgSO_4$ (n=8)	Diazepam (n=12)	Relative risk	95% CI
Apgar score				
<7 at 1 min	3 (38)	11 (92)	0·4	0·2 to 1·0
<7 at 5 min	2 (25)	6 (50)	0·5	0·1 to 1·9
Stillbirth	0	2		
Livebirth	8	10		
Early neonatal death	1	0		
Intubated	1 (13)	6 (50)	0·3	0·04 to 1·7
Admitted to neonatal intensive care unit	5 (63)	9 (75)	0·8	0·5 to 1·6
Days on neonatal unit Median (range)	7 (0–28)	6·5 (0–29)		
Length of stay >7 days	2	3	1·0	0·2 to 4·7

Results are n (%)

lem with magnesium sulphate therapy. Cardiac arrest associated with an intravenous bolus injection of magnesium sulphate is a recognized problem (McCubbin & Sibai 1981; Pritchard *et al.* 1984; Richards *et al.* 1985), usually because there is departure from a standardized protocol. Where this occurred in one of our patients the intravenous injection was faster than recommended. The guidelines for therapy should be adhered to rigidly if such complications are to be avoided. Pritchard *et al.* (1984) advise that intravenous injection of magnesium sulphate should be 'no faster than 1 g/min'.

Renal output was significantly better with magnesium sulphate as fewer women had a diminished urine output within the first 12 h after delivery. Although the mode of action of magnesium sulphate is incompletely understood, beneficial increases in renal and uterine blood flow may occur.

The one maternal death in the study occurred in a woman allocated to magnesium sulphate therapy, but the cause of death was related to anoxia from a cardiorespiratory arrest sustained during transfer with a diazepam drip and before any magnesium sulphate had been given.

The outcome for the fetus also appeared better in the magnesium sulphate group. Significantly fewer infants had depressed Apgar scores. There was less need for intubation at birth and fewer babies required admission to the neonatal intensive care unit in this group, but none of these differences was statistically significant.

Because 67% of the women in the trial had received diazepam before entry to the study, secondary analyses stratified by prior use of diazepam were conducted to investigate this factor. These analyses suggested that magnesium sulphate was preferable to diazepam whether or not diazepam had been given before entry to the trial.

Conclusions are limited by the trial's size and by the fact that most women had already been treated with diazepam before entry to the trial. Further randomized controlled trials are now needed to clarify the place of magnesium sulphate, diazepam, and other anticonvulsants, such as phenytoin, in the management of eclampsia.

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Effectiveness of ultrasound determination of fetal abdominal circumference and fetal ponderal index in the diagnosis of asymmetrical growth retardation

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Summary. A total of 310 unselected women attending an antenatal clinic was screened for growth retardation by ultrasound between 34 and 36 weeks gestation, by measuring the fetal abdominal circumference (AC) and femoral length (FL), from which the 'fetal ponderal index' (AC/FL) was calculated. Asymmetrical growth retardation in the newborn was assessed by Rohrer's ponderal index and the mid-arm/occipito-frontal circumference (MAC/OFC) ratio within 72 h of birth, a neonatal ponderal index or MAC/OFC ratio below the 10th centile being considered abnormal. The sensitivities of an AC below the 25th centile in identifying a birthweight, neonatal ponderal index or MAC/OFC ratio below the 10th centile were 86, 62 and 67% respectively, the specificities being 80, 78 and 76%. The sensitivities of a fetal ponderal index below the 25th centile in identifying a neonatal ponderal index or MAC/OFC ratio below the 10th centile were 52 and 47% respectively, the specificities being 77 and 77%. A possible reason for the poor performance of the fetal ponderal index is discussed.

Intrauterine growth retardation (IUGR) due to uteroplacental insufficiency is an important cause of perinatal death and physical and mental handicap (Fancourt *et al.* 1976; Fitzhardinge & Steven 1972), but the antenatal diagnosis of this condition remains a problem. Even after birth the definition of IUGR presents difficulties; it is now clear that birthweight alone is an unsatisfactory definition of IUGR since it is poorly correlated with perinatal problems. Indicators of asymmetrical IUGR in the newborn such as the ponderal index and the ratio of the mid-arm and occipito-frontal circumferences (MAC/OFC) are more strongly associated with birth asphyxia and neonatal hypoglycaemia than low birthweight (Walther & Ramaekers 1982*a,b*; Jarai *et al.* 1977; Patterson & Pouliot 1987). Previous studies of screening for IUGR by ultrasound have used birthweight as the diagnostic criterion for IUGR, usually selecting the 10th centile as the cut-off point (Pearce & Campbell 1987), although some authors prefer the 5th centile (Neilson *et al.* 1980). Birthweight is easily and accurately measured, but has the disadvantages of overdiagnosing IUGR in symmetrically small babies whose birthweight is < 10th centile, and underdiagnosing IUGR in asymmetrically proportioned babies with birthweights > 10th centile. Measurement of the fetal abdominal circumference or area by ultrasound has been shown to predict accurately birthweights < 10th or < 5th centiles (Pearce & Campbell 1987; Neilson *et al.* 1980), but there has been no study to

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Table 1. Centiles of fetal abdominal circumference (mm) and ponderal index

	Fetal abdominal circumference (mm) for gestation (weeks)			Fetal ponderal index for gestation (weeks)			
Centile	34 (*n*=100)	35 (*n*=136)	36 (*n*=74)	34 (*n*=100)	35 (*n*=136)	36 (*n*=74)	34–36 (*n*=310)
97	350	355	364	4·86	4·79	4·73	4·80
95	346	351	359	4·80	4·74	4·68	4·74
90	339	345	353	4·71	4·65	4·61	4·66
75	328	335	343	4·55	4·52	4·48	4·52
50	316	325	332	4·38	4·37	4·35	4·37
25	304	314	321	4·21	4·22	4·21	4·21
10	293	304	311	4·05	4 08	4·08	4·07
5	286	298	305	3·96	4·00	4·01	3·99
3	282	294	301	3·90	3·95	3·96	3·94
Mean	316	325	332	4·38	4·37	4·35	4·37
(SD)	(18)	(16)	(16)	(0·25)	(0·22)	(0·20)	(0·23)

Table 2. Centiles of birthweight

	Birthweight (kg) for gestation (weeks)				
Centile	37 (*n*=23)	38 (*n*=34)	39 (*n*=72)	40 (*n*=90)	41–42 (*n*=78)
97	3·90	4·06	4·33	4·28	4·42
95	3·78	3·94	4·21	4·17	4·33
90	3·59	3·76	4·02	4·02	4·18
75	3·28	3·45	3·70	3·75	3·93
50	2·93	3·12	3·35	3·46	3·65
25	2·58	2·79	3·00	3·17	3·37
10	2·27	2·48	2·68	2·90	3·12
5	2·08	2·30	2·49	2·75	2·97
3	1·96	2·18	2·37	2·64	2·88
Mean	2·93	3·12	3·35	3·46	3·65
(SD)	(0·52)	(0·50)	(0·52)	(0·43)	(0·42)

Table 3. Centiles of neonatal ponderal index

	Neonatal ponderal index for gestation (weeks)					
Centile	37 (*n*=23)	38 (*n*=34)	39 (*n*=72)	40 (*n*=90)	41–42 (*n*=78)	37–42 (*n*=297)
97	2·91	3·02	2·95	3·07	2·97	2·98
95	2·86	2·96	2·90	3·01	2·92	2·93
90	2·78	2·86	2·83	2·91	2·85	2·85
75	2 65	2·70	2·70	2·75	2·72	2·71
50	2·50	2·53	2·56	2·58	2·58	2·56
25	2·35	2·36	2·42	2·41	2·44	2·41
10	2·22	2·20	2·29	2·25	2·31	2·28
5	2·14	2·10	2·22	2·15	2·24	2·20
3	2·09	2·04	2·17	2·09	2·19	2·14
Mean	2·50	2·53	2·56	2·58	2·58	2·56
(SD)	(0·22)	(0·26)	(0·21)	(0·26)	(0·21)	(0·22)

Table 4. Centiles of mid-arm/occipito-frontal circumference (MAC/OFC) ratio

	MAC/OFC ratio for gestation (weeks)				
Centile	37 (*n*=23)	38 (*n*=34)	39 (*n*=72)	40 (*n*=90)	41–42 (*n*=78)
97	0·323	0·330	0·334	0·342	0·336
95	0·319	0·324	0·328	0·337	0·332
90	0·311	0·315	0·320	0·328	0·325
75	0·299	0·301	0·307	0·314	0·313
50	0·286	0·285	0·292	0·299	0·301
25	0·272	0·269	0·276	0·283	0·288
10	0·260	0·254	0·263	0·269	0·276
5	0·252	0·245	0·255	0·261	0·269
3	0·248	0·240	0·249	0·256	0·265
Mean	0·286	0·285	0·292	0·299	0·301
(SD)	(0·021)	(0·024)	(0·023)	(0·023)	(0·019)

Table 5. Efficiency of 25th centile fetal abdominal circumference in identifying birthweight, neonatal ponderal index and mid-arm/occipito-frontal circumference (MAC/OFC) ratio below the 10th centile

	Birthweight	Neonatal ponderal index	MAC/OFC ratio
Sensitivity	24/28 (86%)	18/29 (62%)	20/30 (67%)
Specificity	215/269 (80%)	208/268 (78%)	202/267 (76%)
Positive predictive value	24/78 (31%)	18/78 (23%)	20/80 (25%)
Negative predictive value	215/219 (98%)	208/219 (95%)	202/217 (93%)

Table 6. Efficiency of 25th centile fetal ponderal index in identifying neonatal ponderal index and mid-arm/occipito-frontal circumference (MAC/OFC) ratio below the 10th centile

	Neonatal ponderal index	MAC/OFC ratio
Sensitivity	15/29 (52%)	14/30 (47%)
Specificity	208/268 (77%)	208/267 (77%)
Positive predictive value	15/75 (20%)	14/73 (19%)
Negative predictive value	208/222 (94%)	208/224 (93%)

our knowledge which has investigated the use of ultrasound as a screening test for asymmetrical IUGR.

Subjects and methods

A total of 310 unselected women attending an antenatal clinic had ultrasound estimations of fetal abdominal circumference (AC) and femoral length (FL) made once only between 34 and 36 weeks gestation. At this ultrasound examination AC and FL were measured twice, and the mean of the measurements obtained was used for analysis. All the ultrasound measurements were made by one of the authors (P.S.), who had had many years' experience of the technique.

The fetal ponderal index was calculated from the ratio of the abdominal circumference to the femoral length (AC/FL). The logic of this formula is that in asymmetrical IUGR the length of the fetus is well preserved while the soft tissue mass is depleted. Thus symmetrically grown fetuses should have a normal weight–length ratio, whereas in asymmetrical fetuses the weight–length ratio should be diminished. The only somatic fetal length measurement which can be made with real-time equipment is femoral length. Fetal abdominal circumference is strongly associated with fetal weight; therefore the ratio of abdominal circumference (AC) to femoral length (FL) is a weight–length ratio, analogous to the neonatal ponderal index. This explains the use of the term 'fetal ponderal index'.

All patients had previously had gestational age assessed by ultrasound early in pregnancy; only those women with certain gestational age were included in the study. The size of the study chosen was thought to be sufficient to generate enough patients with asymmetrical IUGR (about 30) to be able to demonstrate the usefulness of these ultrasound measurements as screening tests. After birth, the birthweight, crown–heel length, and mid-arm and occipito-frontal circumferences were measured in each baby, and the neonatal ponderal index (Rohrer 1921) and MAC/OFC ratio calculated. The neonatal ponderal index is the ratio of the birthweight in g multiplied by 100, divided by the cube of the crown–heel length in cm.

From the data the following centile charts were constructed: (1) AC at 34, 35 and 36 weeks, (2) fetal ponderal index at 34, 35 and 36 weeks; (3) birthweight for each week between 37 and 42 weeks; (4) neonatal ponderal index at 37–42 weeks, and for each week separately; (5) MAC/OFC ratio for each week between 37 and 42 weeks.

Since this was an investigation of the usefulness of AC and the fetal ponderal index as *screening* tests for asymmetrical IUGR, it was thought reasonable to select the 25th centile as the cut-off point for these ultrasound measurements. This implies that, if the tests were useful, 25% of the whole obstetric population would be identified to be at risk of asymmetrical IUGR, requiring more detailed assessment by ultrasound or biophysical tests. In view of the potentially devastating consequences of missing IUGR, the 25th centile seemed to be an appropriate cut-off point to choose. The traditional 10th centile of neonatal ponderal index and MAC/OFC ratio were selected to define abnormality, even though it has not yet been established whether the 10th, 5th, or 3rd centiles may most effectively define a group of babies at risk of perinatal problems.

Results

Thirteen women were delivered before 37 weeks and were excluded from the study which was restricted to term deliveries (37–42 weeks); the data from 297 patients were therefore analysed.

Table 1 demonstrates the centile values of AC and fetal ponderal index for each week between 34 and 36 weeks. AC is strongly dependent on gestational age, whereas, at least between 34 and 36 weeks, the fetal ponderal index is independent of gestational age. In Tables 2–4 the centile values of birthweight, neonatal ponderal index and MAC/OFC ratio are shown for each week between 37 and 42 weeks. Birthweight is strongly dependent on gestational age, whereas neonatal ponderal index is independent of gestational age, at least in these term infants. MAC/OFC ratio also depends upon gestational age. In the analysis of the data we therefore grouped the fetal and neonatal ponderal indices but analysed AC, birthweight and MAC/OFC ratio for each week separately.

Table 5 shows the sensitivities, specificities and predictive values of AC below the 25th centile in identifying birthweight, neonatal ponderal index and MAC/OFC ratio below the 10th centile. In Table 6, the sensitivities, specificities and predictive values of fetal ponderal index below the 25th centile in identifying neonatal ponderal index and MAC/OFC ratio below the 10th centile are shown.

Discussion

This study demonstrates that fetal abdominal circumference, birthweight and MAC/OFC ratio are strongly dependent on gestational age, whereas the fetal ponderal index between 34 and 36 weeks and neonatal ponderal index after 37 weeks are not, which justifies the grouping of these indices (Tables 1–4). The independence of the neonatal ponderal index of gestational age after 37 weeks has already been reported (Miller & Hassanein 1971; Miller 1979). Our study confirms that finding. The neonatal ponderal indices in the present study are very similar to those reported by Miller & Hassanein (1971), the 10th centile value in that study being 2·32 and in ours 2·28 The MAC/OFC ratios in our study are very similar to those quoted by Meadows *et al.* (1986), the 10th centile value for grouped gestational ages between 37 and 42 weeks in that study being 0·26 and in ours 0·254–0·276. Fetal and neonatal ponderal index are independent of gestational age near term because increase in fetal weight occurs *pari passu* with increase in fetal length. In contrast, the soft tissue of the fetal arm near term grows progressively, at a time when the growth rate of the head is slowing down; this explains the progressive increase of the MAC/OFC ratio from 37 to 42 weeks.

Since birthweight is known to be strongly associated with fetal abdominal circumference near term (Pears & Campbell 1987; Neilson *et al.* 1980) it is not surprising that in this study AC performed relatively well in identifying babies with birthweights < 10th centile. However, birthweight below the 10th centile is relatively poorly correlated with perinatal problems due to IUGR when compared with measurements of asymmetrical IUGR in the newborn (Jarai *et al.* 1977; Walther & Ramaekers 1982*a*,*b*; Patterson & Pouliot 1987). In this study AC performs poorly in identifying neonatal ponderal index below the 10th centile: the sensitivity was 62%, specificity 78% and the predictive value of a positive test 23%. AC also performs badly in identifying MAC/OFC ratio below the 10th centile: the sensitivity was 67%, specificity 76% and the predictive value of a positive test was 25%. Thus AC cannot be recommended as a screening test for the identification of asymmetrical growth retardation.

Fetal ponderal index fares even worse; the sensitivity of the fetal ponderal index in identifying neonatal ponderal index below the 10th centile was 52%, the specificity 77% and the predictive value of a positive test 20%. The sensitivity of the fetal ponderal index in identifying MAC/OFC ratio below the 10th centile was 47%, the specificity 77% and the predictive value of a positive test 19%.

In theory, the fetal ponderal index should be more efficient than AC alone in diagnosing asymmetrical growth retardation, yet AC is just as good if not better. One possible reason for this may be that the actual ultrasound and neonatal measurements were inaccurate. After the present study was completed the authors performed a repeatability study of all these measurements. Inter-observer variation was assessed by the method of limits of agreement described by Bland & Altman (1986). The limits of agreement of ultrasound measurement of abdominal circumference were −2·2 to +2·0 cm and femoral length were −7·4 to +4·9 mm; these limits were found to be unacceptably wide (Sarmandal *et al.* 1989), whereas the limits of agreement of the neonatal measurements were very close. Since the fetal ponderal index is the ratio of two measurements, it is not surprising it performed badly as a screening test for asymmetrical growth retardation. We presume therefore that the hitherto unforeseen effect of inter-observer variation, a manifestation of the inherent difficulty in performing a particular measurement, is the main reason for the poor performance of the fetal ponderal index.

In conclusion, ultrasound measurement of abdominal circumference and the 'fetal ponderal index' are not useful as screening tests for the identification of asymmetrical growth retardation, and the search for such a test must continue. One of the problems with studies of screening for IUGR (including this one) is the choice of an arbitrary centile cut-off point in the definition of IUGR. It may be that this centile concept is inappropriate, since there will always be some infants above the cut-off centile at risk of perinatal problems of uteroplacental insufficiency, and some below the cut-off centile who are at no risk of such perinatal problems. The very term 'intrauterine growth retardation' is unfortunate, since it has focused obstetricians' minds unduly on the size of the baby, and not on the real problem, uteroplacental insufficiency. Future research should be directed into methods of screening for uteroplacental insufficiency, using important perinatal events as the end-points of such screening, such as birth asphyxia, neonatal convulsions, hypoglycaemia and polycythaemia, and not an arbitrary centile as the end-point.

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Malignant melanoma of the vulva: a clinicopathological study of 50 women

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Summary. A clinicopathological review of 50 primary malignant melanomas of the vulva in the West Midlands region of England is presented. The overall 5-year-survival rate was 35%, when adjusted for age. Significant predictors of survival were clinical stage, patient age, tumour ulceration, cell type and mitotic rate. Tumour thickness was of prognostic importance but as a prognostic variable it did not operate independently of stage and as most lesions were deeply invasive at presentation vulval tumours must be separated for prognostic purposes into bands at greater overall thicknesses than those used for skin melanomas generally. There was no significant relation between survival and type of surgery performed as a primary therapeutic procedure.

Malignant melanoma of the vulva is an uncommon disease which has been said to account for 3 to 7% of all melanomas in women and 8 to 11% of all malignant tumours of the vulva (Silvers & Halperin 1978). The figures for the West Midlands region of England are rather different, here it accounts for 2·2% of all melanomas in women and 3·6% of all vulval malignant tumours. Nevertheless, it is the second commonest primary vulval malignancy, after squamous carcinoma. It is a generally held belief that it is a highly malignant disease with a tendency to both recur locally and develop distant metastases. Five-year-survival rates have varied from 13 to 55% in a number of reported series (Das Gupta & D'urso 1964; Pack & Oropeza 1967; Yackel *et al.* 1970; Morrow & Rutledge 1972; Chung *et al.* 1975; Karlen *et al.* 1975; Edington & Monaghan 1980; Ariel 1981; Bouma *et al.* 1982; Phillips *et al.* 1982; Podratz *et al.* 1983).

Clinical staging of vulval melanoma has not been found to correlate well with survival in some reports (Phillips *et al.* 1982; Podratz *et al.* 1983), though Johnson *et al.* (1986) found it to be useful. Survival of patients with cutaneous malignant melanomas generally has been found to correlate best with the histological staging methods of level of invasion (Clark *et al.* 1969) and tumour thickness (Breslow 1970). Several studies (Chung *et al.* 1975; Phillips *et al.* 1982; Podratz *et al.* 1983; Jaramillo *et al.* 1985; Johnson *et al.* 1986; Beller *et al.* 1986; Benda *et al.* 1986; Itala *et al.* 1986) have applied these methods to vulval melanomas and have found them to be useful prognostic determinants, but the relatively small patient numbers in these series (44, 18, 48, 16, 19, 14, 16 and 9 women respectively) has hampered statistical assessment.

Other histological factors which have been reported to affect prognosis in vulval melanomas are tumour growth pattern, i.e. whether lentiginous, superficial spreading or nodular (Chung *et al.* 1975; Podratz *et al.* 1983; Beller *et al.* 1986) and cell mitotic rate (Johnson *et al.* 1986). In this

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study we have carried out a retrospective clinical and histological review of 50 women with primary malignant melanoma of the vulva in the West Midlands region of England to investigate potential prognostic indicators.

Subjects and methods

Women presenting with primary malignant melanoma of the vulva within the area of the West Midlands Regional Health Authority between 1957 and 1982 were identified from the files of the Regional Cancer Registry (RCR). The female population of this area is 2·6 million. In 49 cases histological material was available for review. A further eight were recorded at the RCR but were excluded from this study. In six of these excluded cases, histological sections were not available. One specimen previously diagnosed as 'amelanotic melanoma' was felt on histological review to be a malignant lymphoma. In another case an autopsy diagnosis of a vulval primary was made when the woman had presented with metastatic melanoma in the groin, but this was not unequivocally confirmed histologically.

A further five women with vulval melanoma were identified from the files of the Birmingham and Midland Hospital for Women (WHB) between 1950 and 1956. Histological material was only available for one of these women, and this was included in this study, bringing the total number to 50.

Tumours arising on the perineum, the urethral mucosa and the vaginal mucosa above the hymenal ring were not included in this study. Tumours arising on the mons pubis were also excluded.

Clinical features examined

For most subjects clinical data were obtained from the files of the RCR, but some hospital records were also reviewed. The data recorded were age, presenting symptoms, tumour location and size, clinical stage, lymph node status, primary and subsequent therapeutic procedures, follow-up information, including date of recurrences and survival.

Tumour size had been recorded for most of the women in either the clinical or pathological reports; where this was not recorded, an estimate was made from the microscopic slides where these included the whole cross-section of the primary lesion.

Clinical staging was retrospective according to the FIGO (1971) classification for vulval carcinomas.

The clinical condition of the lymph nodes was not recorded for many of the women and this was assumed to imply that the nodes were not clinically involved. In five women staging was adjusted when histological examination had detected lymph node metastases. Those with superficial (i.e. inguinal and femoral) lymph node involvement were allocated to stage III and with deep pelvic node involvement to stage IV. Other workers (Podratz *et al.* 1983) have used histological findings in staging and we justify it on the basis that it gives a more accurate description of the extent of disease at presentation.

In non-survivors the cause of death was obtained from copies of the death certificates.

Histological features examined

For most women review involved only sections of the primary lesion. In these, data on metastatic or recurrent disease were obtained from pathology reports.

Two subjects were included for whom sections of the primary lesion were no longer available. However, the diagnosis of malignant melanoma was confirmed in satellite nodules or lymph node metastases and the primary lesion on the vulva was identified unequivocally in both the clinical and pathological reports.

The following criteria were assessed, by two authors (M.G.B. and T.P.R.):

Tumour thickness. This was measured as the distance between the granular cell layer and the deepest point of invasion of the tumour, as defined by Breslow (1970). Measurements were made, to the nearest 0·1 mm, using the Vernier scale of a microscope stage.

Clark's level of invasion. This was estimated as defined by Clark *et al.* (1969). Chung *et al.* (1975) reported that in certain areas the vulval epithelium lacked a well-developed papillary dermis and therefore modified Clark's staging system. We have kept to the original method and as almost all our tumours were deeply invasive (levels IV or V) there was no difficulty in staging.

Growth pattern (or lesion type). This was classified as lentigo maligna, acral lentiginous, superficial spreading and nodular as described previously (Clark *et al.* 1969; McGovern 1970; Clark *et al.* 1975; Coleman *et al.* 1980).

Presence or absence of ulceration. Ulceration was defined as the loss of part or whole of the epidermis overlying the tumour and replacement by an inflammatory cell exudate (McGovern *et al.* 1982).

Presence or absence of a polypoid configuration. Polypoid lesions were either pedunculated or sessile with a broad base and were distinguished from flat or dome-shaped lesions (McGovern *et al.* 1983).

Cell type. This was classified as predominantly epitheloid, predominantly spindle celled or mixed when both cell types were present in roughly equal proportions. This was assessed on the primary lesion only, except in the two cases where these were not available.

Mitotic rate. The rate was obtained by counting the number of tumour cells with mitotic figures in 10 high-power fields (HPF) on three occasions using a ×63 objective on a Leitz Orthoplan microscope (final magnification ×630) and averaging the result to give the result per 10 HPF. Performed on the primary lesions only again excepting the two cases where only metastatic tissue was available.

Lymphocytic inflammatory cell host response. This was graded as minimal (1+), moderate (2+) or marked (3+) as follows: 1+ = cellular infiltrate absent or confined to the margins of the tumour; 2+ = cellular infiltrate more marked than above and present as a discontinuous band beneath the base of the tumour; 3+ = a heavy unbroken band-like infiltrate beneath the base of the tumour.

The degree of melanin pigmentation was not estimated, as assessment is purely subjective and difficult to quantify.

Statistics

Survival curves were drawn up using a method of age adjustment which is based on OPCS English Life Tables and has been fully described previously by Matthews *et al.* (1987). Differences between groups were analysed using standard χ^2 and *t*-tests (Bradford Hill 1984). Confidence intervals (CI), where quoted, are those for the percentage difference in survival. The independent effects of the clinical and histological features were evaluated by a stepwise Cox regression analysis using a BMDP program (Cox 1972; Hopkins 1983).

Results

Clinical features

Of the 50 women studied 45 are dead at the time of writing. In 35 this was recorded as being due to malignant melanoma. Nine died of unrelated causes with no evidence of recurrent melanoma. These were not censored in the analysis because this is not needed when using an age adjustment method. In one woman the cause of death was recorded as 'carcinomatosis' with the primary site unspecified. Five women are still alive with no evidence of recurrent disease. In one the follow-up period is between 4 and 5 years but the other four have been followed up for periods ranging between 6 and 25 years. The longest disease-free interval between primary treatment of vulval melanoma and death is 15 years. In one woman the disease recurred 10 years after treatment and she was dead within 12 years.

The 5- and 10-year-survival rates, when adjusted for age, were 35% and 22% respectively (crude rates = 30% and 15%) with a median survival of 23 months.

Effect of age. The mean age at diagnosis was 63·7 years (SD 15·3 years; range 22–93 years). Only two patients were below 40 years and the peak occurrence was during the eighth decade. Half the women were ⩾65 years and survival in this group was significantly worse than in the younger women, the 5-year-survival rates being 16% and 44% respectively ($t = 2{\cdot}16$, $P<0{\cdot}05$, 95% CI 2 to 54). To compensate for the increased deaths from other causes in older women, age-adjusted rates were calculated. The 5-year rates were 22% for women ⩾65 years of age compared with 45% in those <65 years. This difference was not statistically significant.

Presenting symptoms. Table 1 shows the type and frequency of these. Many women had multiple symptoms and these have been included in the numbers. The commonest presenting complaint was of a 'lump' or 'spot' on the vulva. Bleeding, discharge and pruritus were also commonly reported. 'Other' symptoms included in the table were nocturia, pain on micturition, weight loss, headache and vomiting. One woman had a groin swelling before the appearance of a vulval mass and in another the tumour was found on examination when she was admitted for investigation of gastrointestinal symptoms. The duration of symptoms in general varied from 3 weeks to 18 months. One woman had had a 'mole' all her life (71 years) which had then increased in size over a few months. In 12 the duration of symptoms was not specified.

Tumour location. This is shown in Table 2. Two

Table 1. Type and frequency of presenting symptoms

Presenting symptom	*n*
Vulval lesion	36
Bleeding	21
Discharge	10
Pruritus	6
Ulceration	2
Pain	2
Other	7

lesions arising on the labia minora were also stated to be involving the clitoris. One lesion arising on the clitoris was also involving the labium majus on one side. For 10 women the precise site on the vulva was not specified in the records but in two of these the lesion was stated to be involving the vagina in continuity.

Clinical stage. Figure 1 shows the relation between FIGO stage and survival. Only one woman had a Stage IV tumour. She died within 1 year of diagnosis and is not included in the figure. The age-adjusted 5-year-survival rates were: Stage I = 58%, Stage II = 55%, Stages III and IV = 0%. Staging was not possible in two women. A very highly significant difference was found when grouping Stages I and II together (57% survival) and comparing with Stages III and IV ($t = 4{\cdot}08$, $P<0{\cdot}001$, 95% CI 29 to 84·6). However, those with Stage II disease fared only marginally worse than Stage I and then only after the first 4 years.

Lymph node involvement. Overall, 15 women had histologically proven lymph node metastases at presentation. A further three women had clinically involved nodes but underwent biopsy or local excision only of the primary lesion, of whom one had disseminated disease. Of these 18 women, 17 were dead at the end of 2 years and none survived more than 5 years. The age-adjusted 5- and 10-year-survival rates in the group without lymph node metastases were 55% and 35%.

Table 2. Location of primary vulval melanoma

Location	*n*
Labia majora	16
Labia minora	12
Clitoris	7
Peri-urethral	2
Fourchette	1
Vestibule and vaginal introitus	2
Site not specified	10

Surgery. Table 3 shows the various types of surgical procedures used as primary therapy. Local excision was accompanied by bilateral groin dissection in three women and in one was followed by radical vulvectomy after 5 months, after a recurrence of disease in the groin. Radical vulvectomy was accompanied by bilateral groin dissection in eight women, with biopsy of a femoral node in one and by dissection of the deep pelvic nodes in five There appeared to be a slightly improved survival in the radical vulvectomy group when compared to local excision but this was not statistically significant (age-adjusted 5-year-survival 65% *vs* 52% for Stages I and II, no survivors in either group for Stages III and IV).

Other therapeutic procedures. One woman received radiotherapy along with local excision of the primary lesion and bilateral groin dissection as a primary therapeutic procedure. Ten women received radiotherapy as palliative treatment for lymph node recurrences. Chemotherapy was given to five women with recurrent or disseminated disease.

Histological features

Tumour thickness. Table 4 shows the distri-

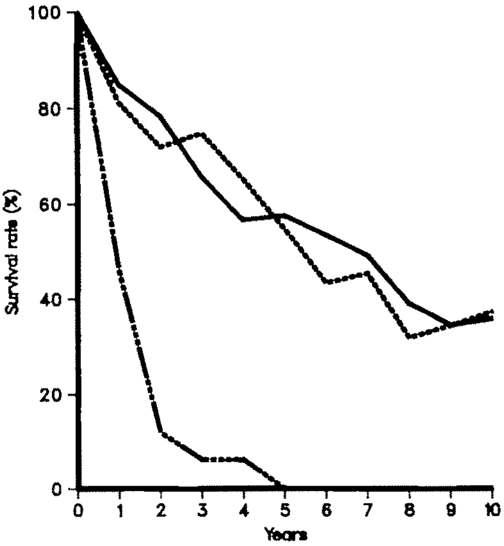

Fig. 1. Annual age-adjusted survival rates by stage. ——— stage I ($n = 22$); ----- stage II ($n = 9$); —··—·· stage III ($n = 18$).

Table 3. Primary surgery for vulval malignant melanoma

Surgery	n
Local excision	18
Biopsy only	2
Radical vulvectomy	22
Simple vulvectomy	2
Partial/hemi-vulvectomy	3
Vulvectomy with urethrectomy and vaginectomy	1
Vulvectomy (type of procedure not specified	2

bution by tumour thickness. The table includes three women in whom the primary lesion was not completely excised but tumour in the biopsy was more than 4·0 mm thick. In four others the thickness could not be measured. The mean thickness for the group was 7·45 mm (SD 5·18). Most women presented with lesions >4·0 mm in thickness. None had lesions <0·75 mm, which in the skin is associated with an excellent prognosis (Breslow 1970). Two women had lesions measuring 0·9 and 1·0 mm thick and these are both long-term survivors, but another, with a lesion 1·3 mm thick, died within 2 years from recurrent disease. For the purposes of statistical analysis, survival curves were drawn up using three bands: 0–4·0 mm, 4·1–8·0 mm and >8 mm (Fig. 2) and the age-adjusted 5-year-survival rates were 59·3%, 38% and 10% for the three bands, respectively. Prognosis therefore worsened with increasing tumour thickness, this trend was statistically significant ($P<0\cdot05$).

Clark's level of invasion. The age-adjusted 5-year-survival rates were: level II = 100% (2 women), III = 0% (2 women), IV = 41% (32 women), V = 17% (7 women). No tumours were classified as level I and overall seven women could not be staged histologically. There were no statistically significant differences between the different levels of invasion but the small number of level II and III lesions precluded meaningful analysis. The two women with level II lesions were, however, both long-term survivors and both had thin lesions, ≤1·0 mm in depth.

Table 4. Distribution of tumour thickness

Tumour thickness (mm)	n
0–0·75	0
0·76–1·5	3
1·6–4·0	10
4·1–8	19
>8	14
Unclassified	4

Lesion type (growth pattern). In the present series 28 invasive tumours were superficial spreading (SS), 14 were nodular (N) and eight could not be classified. No acral lentiginous lesions were seen. One lesion had some of the classical features of lentigo maligna but this was associated with an invasive SS tumour at another site on the vulva and has been classified under that heading. In two women there was histological evidence of a pre-existing benign naevus in association with an SS lesion. One woman with an early invasive SS lesion had histological evidence of tumour regression. Statistically there was no significant difference in survival between the two types of growth pattern (age-adjusted 5-year-survival: 41·2% for SS, 41·6% for N).

Ulceration. Most lesions were found to be ulcerated ($n = 35$). Two could not be classified, but the ulcerated group includes one in which the primary lesion was not available for review but had been reported previously as ulcerated. Figure 3 shows the survival curves for the two groups. Ulcerated tumours had a significantly worse prognosis ($t = 2\cdot29$, $P<0\cdot05$, 95% CI 5 to 67). Age-adjusted 5-year-survival rates were 62% for non-ulcerated and 27% for ulcerated

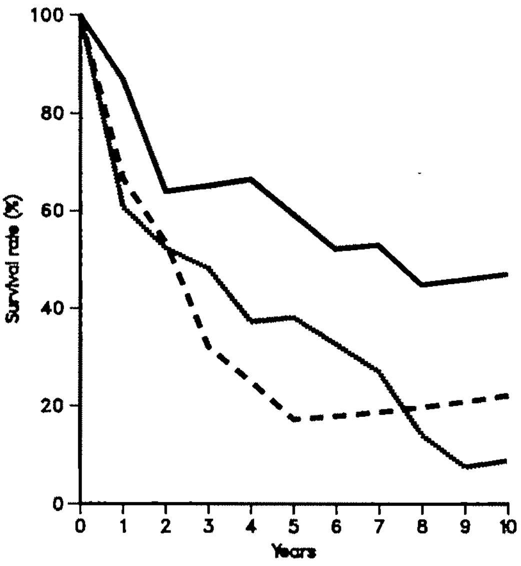

Fig. 2. Annual age-adjusted survival rates by tumour thickness ——— 0–4·0 mm ($n = 13$); ······ 4·1–8 mm ($n = 19$);——— >8 mm ($n = 14$).

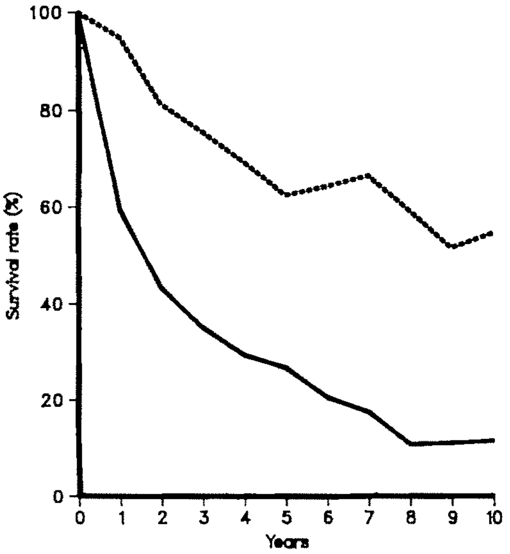

Fig. 3. Annual age-adjusted survival rates and ulceration. ——— ulcerated ($n = 35$); ···· not ulcerated ($n = 13$).

tumours. It was noticed that tumours which were not ulcerated had a significant positive association with a low mitotic rate and a mixed cell type ($P<0{\cdot}01$).

Polypoid configuration. Polypoid and non-polypoid tumours were present in roughly equal proportions. Four tumours could not be classified, but the polypoid group contains one tumour where the sections available were incomplete but which had been macroscopically described as polypoid. There was no statistically significant difference between the two groups (age-adjusted 5-year-survival for non-polypoid group 33% (24 women), polypoid group 44% (22 women)). Survival was slightly better in the polypoid group up to 7 years, but after that there were proportionately more survivors in the non-polypoid group.

Cell type. As shown in Fig. 4, survival was significantly poorer in the epithelioid cell group when compared with the other two groups combined ($t = 2{\cdot}1$, $P<0{\cdot}05$, 95% CI 1 to 58). Age-adjusted 5-year-survival rates were: spindle cell = 48%, mixed = 43%, epithelioid = 15%.

Mitotic rate. This is shown in Fig. 5. Tumours with a low mitotic rate (<5/10 HPF) had a significantly better prognosis when compared with all other bands combined ($t = 2{\cdot}3$, $P<0{\cdot}05$, 95% CI 2 to 54). Above 5 mitoses per 10 HPF there was no relation between mitotic rate and survival. Age-adjusted 5-year-survival rates were 57% for the 0–4/10 HPF group (16 women) and 24% for 5 or more/10 HPF (34 women). The mean mitotic rate for the whole group was 9·1 (SD 7·6). Low mitotic rate was associated with non-ulcerated tumours ($P<0{\cdot}05$).

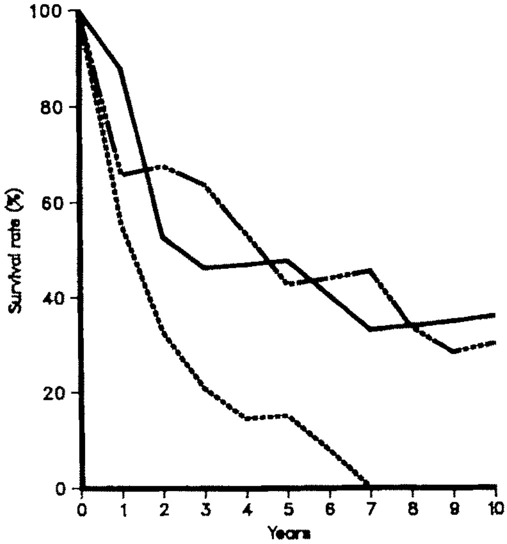

Fig. 4. Annual age-adjusted survival rates by cell type. ——— spindle cell ($n = 14$); ——— epithelioid ($n = 17$); —·—··· mixed ($n = 19$).

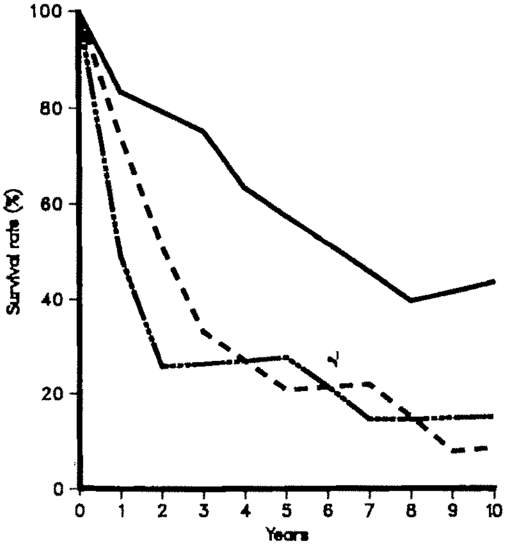

Fig. 5. Annual age-adjusted survival rates by mitotic rate. ——— 0–4/10 HPF ($n = 6$); ——— 5–9/10 HPF ($n = 17$); —·—··· 10+/10 HPF ($n = 17$).

Table 5. Cox models

Model	Step and d.f.	Covariate entered	Approximate χ^2 improvement	*P*-value	High risk associated with
I	1	Stage	9·1	0·003	High stage
	2	Cell type	6·6	0·01	Epithelioid type
	3	Age	3·7	0·06	High age
	4	Ulceration	5·3	0·02	Ulcerated
II	1	Stage	16·7	0	High stage
	2	Mitotic rate	6·6	0·01	High rate
	3	Age	3·4	0·06	High age
	4	Ulceration	4·3	0·04	Ulcerated

Lymphocytic cell host response. Survival showed a weak association with the degree of lymphocytic infiltration but the differences were not statistically significant. A marked lymphocytic cell host response tended to be associated with lesions which were relatively thin and non-polypoidal in form ($P<0{\cdot}05$ for both).

Cox regression analysis

The variables used in the stepwise analysis were age, stage, thickness, Clark's level, ulceration, lesion type, cell type, lymphocytic infiltration and mitotic rate. Complete data were available for 40 women. The rule for entering a covariate was ($P<0{\cdot}1$) and for removing ($P>0{\cdot}15$). The proportionality assumption of risk was checked by stratification by each of the variables. The small numbers made this inconclusive but 'polypoidal configuration' appeared to violate this and was omitted from the model.

At step 0, age, stage, thickness, ulceration, cell type and mitotic rate were all significant prognostically and lymphocytic infiltration was borderline. At step 1, stage (approximate χ^2 to enter = 9·1) was entered into the model, low stages being associated with low risk. Thickness and lymphocytic infiltration were then no longer significant. At step 2, cell type (approximate χ^2 to enter = 6·6) was entered into the model, spindle cell type being associated with low risk. In two further steps, age and ulceration were entered into the model, older patients and ulcerated tumours being associated with high risk. Mitotic rate ceased to be significant when cell type was entered.

In an effort to bring more of the women into the analysis, only stage, cell type, age, mitotic rate and ulceration were used and the process repeated for 48 women. Table 5 summarizes the results.

Although a closer model may be possible by further adjusting scales of the covariates these results imply that stage is the most significant independent prognostic indicator. After controlling for stage, mitotic rate and cell type are both important but not independently. Ulceration is also significant and age just fails to reach significance ($P=0{\cdot}06$).

Discussion

This study has confirmed the overall poor prognosis of primary malignant melanoma of the vulva. The age-adjusted 5-year-survival rate of 35% is comparable with rates reported previously (Das Gupta & D'urso 1964; Pack & Oropeza 1967; Yackel *et al.* 1970; Ragni & Tobon 1974; Chung *et al.* 1975; Ariel 1981; Phillips *et al.* 1982) Poor survival is related to the advanced stage of disease at presentation and to the age group under study. Age has been found to be a prognostic determinant in cutaneous melanomas by other workers (Huvos *et al.* 1974; Shaw *et al.* 1980; Rampen *et al.* 1980). The mean age of 63·7 years in this series compares with that of 46 years in one reported series of cutaneous melanomas (Elias *et al.* 1977) and in the present study women aged ≥65 years fared worse than the under 65s. The older group tended to have thicker tumours and therefore part of the reason for the poorer survival is their late presentation.

FIGO staging was found to be important, but only when comparing Stages I and II combined against III and IV. No significant difference was demonstrated between Stages I and II. This is in keeping with the findings of other workers (Podratz *et al.* 1983). The surface diameter measurements applied in staging of the primary lesion would therefore not appear relevant, the important factor being spread of disease beyond the confines of the vulva, particularly to the regional lymph nodes. Our findings confirm those in earlier reports that the development of lymph node metastases is an ominous sign (Das Gupta & D'urso 1964; Yackel *et al.* 1970; Morrow & Rutledge 1972; Edington & Monaghan 1980; Ariel 1981).

This series emphasizes the importance of incorporating histological findings in determining the extent of disease with particular reference to assessing lymph node status. Of 37 patients five (13%) were found to have nodes histologically positive for metastatic melanoma which had not been recorded clinically. Other workers (Das Gupta & D'urso 1964; Podratz *et al.* 1983) have reported discrepancies in the region of 30% between clinical and histological findings, and therefore microscopic assessment is necessary for accurate staging.

We have not found the histological staging methods described by Breslow (1970) and Clark *et al.* (1969) to be useful prognostically, but this is because most of our lesions fell into poor prognosis groups—>4·0 mm thick (van der Esch *et al.* 1981) and Clark's level IV and V. Bagley *et al.* (1981) have defined all lesions at cutaneous sites more than 1·5 mm thick and Clark's level IV or more to be high risk.

In this series from simple observation it appears likely that lesions up to 1 mm thick and Clark's level I or II have a favourable prognosis. Essentially these findings are in accordance with those of Chung *et al.* (1975). However, Bailet *et al.* (1987) reported a vulval tumour 0·75 mm thick and Clark's level II which developed distant recurrences 2 years after treatment and it is clear that the behaviour of malignant melanoma can be unpredictable. In our series, thickness tended to be associated with clinical stage, but we identified a group of tumours more than 8 mm thick which had a particularly poor survival.

Tumour ulceration has been found to be an important prognostic determinant in this series. This is similar to the findings in cutaneous melanomas (Balch *et al.* 1980; McGovern *et al.* 1982). The adverse effect of ulceration on prognosis in skin melanomas is still apparent after adjusting for tumour thickness and appears to indicate a biologically more aggressive tumour (Balch *et al.* 1980). In vulval tumours, Johnson *et al.* (1986) reported that ulceration was present in most tumours from non-survivors in their series, but otherwise few workers have commented on this aspect of vulval tumours.

Mitotic rate and cell type were also prognostic determinants but were less important than ulceration, and multivariate analysis showed that these factors did not act independently. Johnson *et al.* (1986) reported that mitotic rate was a useful prognostic indicator in vulval melanomas and it is also important in cutaneous tumours (Schmoekel & Braun-Falco 1978). An association was noted in our series between lesions with a low mitotic rate and those which were not ulcerated and this would suggest that this group are inherently less aggressive. The finding that epithelioid cell type carried a poor prognosis is at variance with those of other workers who have found no correlation with cell type (Fenn & Abell 1973; Chung *et al.* 1975; Podratz *et al.* 1983; Johnson *et al.* 1986). The study of a larger number of tumours is desirable.

No statistically significant relation was found between survival and lymphocytic cell host response. Study of a larger series would be necessary before further comment. In cutaneous melanomas generally the presence of a lymphoid response is regarded as a favourable prognostic sign by some (Huvos *et al.* 1974; Day *et al.* 1981). The infiltrate is said to disappear with increasing depth of penetration of the tumour. Our findings are in accordance with this in that a heavy lymphocytic infiltrate was associated with thin and non-polypoidal tumours.

No relation was found between lesion type and survival in our series. Other workers (Podratz *et al.* 1983; Johnson *et al.* 1986) have reported a worse outcome in nodular melanomas, possibly simply because they tend to be thicker. Our negative findings could be explained on the basis that most of the tumours were thick and deeply invasive on presentation. The presence of a polypoid configuration to a tumour was also found to be of no prognostic significance. In cutaneous melanomas polypoid tumours have been associated with a worse outcome (Larsen & Grude 1979; Manci *et al.* 1981; McGovern *et al.* 1983) but this is because they tend to be thick (McGovern *et al.* 1983), again the overall preponderance of thick tumours in our series would account for our negative findings.

Traditionally, malignant melanoma of the vulva has been treated by radical vulvectomy. Davidson *et al.* (1987) have recently questioned this approach. In their series they found that there was no benefit derived from radical or simple vulvectomy when compared to local excision either in local control, disease-free interval or patient survival. In this series we have not found any significant relation between type of surgery performed and patient survival. Local excision alone was compatible with long disease-free intervals and long-term survival even in some women with thick lesions. Assessment is difficult in the present study because a wide variety of procedures was performed in different centres in the West Midlands Region and there was a lack of a uniform or standardized approach. However, for cutaneous melanomas >4·0 mm thick generally the extent of surgery performed has been found to have no significant effect on the subsequent course of the disease (Balch *et al.* 1979). Most of our lesions came into this category and this, and the small numbers involved, may account for the lack of clear benefit from a radical procedure in our study.

This study confirms previous reports of the overall poor prognosis of malignant melanomas of the vulva and indicates that this is mainly due to the advanced extent of the disease at presentation. Clearly we must educate women to apply the same degree of suspicion to pigmented lesions of the vulva as to those elsewhere on the skin. As clinicians we must define those features which allow improved prognostic precision in more advanced tumours in order to tailor therapy to the individual patient.

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A randomized comparison of early with conservative use of antihypertensive drugs in the management of pregnancy-induced hypertension

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Summary. Two treatment strategies were compared in 155 women with pregnancy-induced hypertension who were also given comprehensive non-pharmacological care. The mean gestation at entry was 28 weeks. As long as the diastolic blood pressure (DBP) remained below 106 mmHg, oxprenolol, or oxprenolol plus dihydralazine, were given to the early treatment group, and matching placebos to the control group. Open antihypertensive treatment was provided for patients whose DBP rose above 105 mmHg. Proteinuria occurred in seven women in each group. In the early treatment group, 13 of the 78 women were delivered by caesarean section; the corresponding numbers in the control group were 27 of 76 (17 *vs* 36%, 95% confidence interval (CI) of difference: 5–33%); the sections included seven and 16 in the early treatment and control groups, respectively, for severe hypertension and/or fetal distress. There were five perinatal deaths, two in the early treatment group and three in the control group. Early treatment did not influence gestational age at birth or birthweight. Respiratory distress syndrome occurred in four infants in the early treated group and in 10 in the control group; 14 infants in the former group and 26 in the latter were in hospital for more than 10 days (18 *vs* 35%; 95% CI of difference 4–32%). These results indicate that early antihypertensive treatment with oxprenolol is safe for the fetus and newborn in pregnancy-induced hypertension, but has no advantage over non-pharmacological care in terms of fetal growth. However, it may prevent acute hypertension in late pregnancy and associated fetal distress, and thus reduce the number of caesarean sections.

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Although hypertension is common in pregnancy, the question of which women should be given antihypertensive drugs and at what level of blood pressure has not yet been resolved. To ensure short-term maternal safety, drug therapy is required when the diastolic blood pressure (DBP) exceeds 105–110 mmHg (Redman *et al.* 1976). When the DBP is below 105 mmHg, antihypertensive treatment should aim to ensure fetal and neonatal well-being such as preventing miscarriage or perinatal death and intrauterine growth retardation (IUGR).

That antihypertensive agents can effectively prevent miscarriage, perinatal death or IUGR remains, however, to be established. Administration of methyldopa reduced the frequency of mid-pregnancy miscarriage in women with mild to moderate hypertension in early pregnancy (Leather *et al.* 1968; Redman *et al.* 1976). However, early hypertension affects only a minority of pregnant women (Plouin *et al.* 1986; Redman & Jefferies 1988), and prevention of miscarriage does not apply to the more frequent pregnancy-induced hypertension (PIH), since the latter occurs after 20 weeks gestation. Gallery *et al.* (1979) compared methyldopa with oxprenolol for the treatment of hypertension in pregnancy and found better fetal growth in the group treated with oxprenolol, but Fidler *et al.* (1983), in a larger series, could not confirm these findings. In a placebo-controlled trial of atenolol in mild to moderate PIH, Rubin *et al.* (1983) reported that delivery occurred earlier in the placebo group but the rate of IUGR was similar in the two groups. They noted, however, that all the babies with respiratory distress syndrome were in the placebo group. In an open randomized trial of hospital admission with or without concomitant labetalol therapy in pre-eclampsia, Sibai *et al.* (1987) reported a higher frequency of IUGR in the women given labetalol than in those treated by hospital admission alone.

The present trial was designed to compare two treatment strategies for managing PIH. The first included non-pharmacological care plus administration of antihypertensive agents as soon as the DBP exceeded 84 mmHg, that is, reached levels associated with an increased frequency of IUGR compared with normotensive pregnancies (Friedman & Neff 1977; Plouin *et al.* 1983). In the second strategy, antihypertensive agents were added to non-pharmacological care only for women whose DBP rose above 105 mmHg; that is, they were given later, and only to those few women who developed severe hypertension. The rate of IUGR was chosen as the primary end point, since high DBP levels have been shown in multivariate analysis to be predictive of IUGR (Friedman & Neff 1977; Scott *et al.* 1981; Plouin *et al.* 1983). Oxprenolol was chosen since it has been reported to be more favourable than methyldopa to fetal growth (Gallery *et al.* 1979), and because there is evidence suggesting that it is probably safe for the fetus and newborn (Gallery *et al.* 1979; Fidler *et al.* 1983).

Subjects and methods

The present trial was part of a programme developed in the French Caribbean islands for the screening, assessment and care of pregnancies complicated by hypertension. The study protocol was approved by the National Ethics Committee of the Institut National de la Santé et de la Recherche Médicale, and participants gave informed oral consent to the study.

Patient selection

All 590 hypertensive women seen in the participating maternity hospitals in Pointe à Pitre and Fort de France between January 1984 and June 1987 were screened for inclusion. Eligibility requirements included a singleton pregnancy, the start of follow-up in the participating clinic and a recorded DBP below 85 mmHg before 20 weeks gestation, between 20 and 36 weeks gestation at entry, and DBP exceeding 84 mmHg on two separate occasions after the 20th week. Women with type I diabetes, congestive heart failure, cardiac block or asthma, and those with a history of prepregnancy hypertension or who had taken antihypertensive drugs during their current pregnancy, were not included.

Protocol

Randomization was in stratified blocks of 10 in the two participating hospitals. Each woman who met the inclusion criteria was given a number corresponding to her rank of admission in the trial. This number corresponded to a sealed envelope and to an individual batch of drugs containing either the maximum amount of active drugs that could be used in 20 weeks of treatment or placebos of identical appearance. When the woman had been irrevocably entered in the trial, each batch of treatment was opened by the local investigator (M.D. in Pointe à Pitre and M.E.K. in Fort de France). Each envelope contained information about the nature of the treatment—active or placebo—and was opened only in the cases listed below. All the envelopes were collected at the end of the trial in order to check which treatments had been unblinded. The blinded treatment batches and sealed envelopes had been prepared in Paris by a pharmacist at Ciba-Geigy France, who was not otherwise involved in the trial. Except for the women withdrawn from double-blind treatment in accordance with the study protocol, the treatment code for each woman was not disclosed to investigators, nurses, obstetricians or pediatricians until after the main analysis of the results.

The starting dosage of oxprenolol or matching placebo was 160 mg in two daily doses. Active treatment or matching placebo was titrated to 320 mg of oxprenolol, 320 mg of oxprenolol plus 50 mg of dihydralazine, and finally 320 mg of oxprenolol plus 100 mg of dihydralazine as required to obtain a DBP below 86 mmHg. Treatment was unblinded in the three following cases: major intolerance (in which case treatment was freely adapted by the physician in charge of the patient) and DBP higher than 105 mmHg on two occasions during the same visit, either during the maximum dosage of randomized treatment and no proteinuria, or during any treatment regimen when proteinuria was present. In the last two cases, treatment was open and active drugs were used. For patients previously given active drugs, 0·5 or 1 g of methyldopa daily was added to the oxprenolol and dihydralazine. For patients previously given placebo, the same stepped treatment comprising oxprenolol, oxprenolol plus dihydralazine and then oxprenolol plus dihydralazine plus methyldopa was given, but it was open and the doses were increased every 3 days.

In addition to randomized treatment, women in both groups were provided with non-pharmacological care, including home rest facilities, home management by community midwives, counselling on diet and lifestyle and, when appropriate, bed rest and maternal and fetal monitoring in an obstetric ward. All medical care was free, including drugs, diagnostic tests and hospital visits or admissions. Follow-up examination took place every week when the DBP was above 85 mmHg, and every 2 weeks when it was below 86 mmHg. Patients were admitted to hospital if the DBP exceeded 105 mmHg during treatment, if they had proteinuria, or for other obstetric or fetal indications.

Methods

Blood pressure was measured in the sitting position after 5 min of rest. A mercury manometer with a 13 × 25 cm cuff was used and the DBP was recorded at the muffling of sounds. Proteinuria was considered significant when, on at least two occasions, it was above 1 g/l or a dip-test gave a positive reaction of 2+ or more (Davey & MacGillivray 1986). IUGR was defined as a birthweight below the 10th centile of the expected weight according to Lubchenco *et al.* (1972).

Analysis

From previous data (Bréart *et al.* 1982) it was possible to estimate that the inclusion of over 70 pregnant women in each group would yield a power of 0·95 for the detection of a clinically relevant mean difference of 250 g in term birthweight. Outcome was assessed according to the strategy allocated at randomization. Data are expressed as means (SD). Differences in means were analysed using the two-tailed, unpaired *t*-test. The χ^2-test was applied to qualitative variables with Yates' correction when the expected number was between 5 and 10, and with Fisher's method when it was below 5. The main outcome data are given with 95% confidence intervals (CI).

Results

Baseline data

Of the 155 eligible women, 78 were allocated to the early treatment group and 77 to the control group. The two groups had comparable demographic characteristics, parity, obstetric history, history of hypertension in a previous pregnancy, gestational age and BP at entry (Table 1).

Maternal follow-up

One woman in the control group moved out of the area and was lost to follow-up. At her last visit during the 30th week of pregnancy, her BP was 140/93 mmHg with no proteinuria, and fetal growth was considered normal. Twenty-three patients were withdrawn from blind treatment but not from follow-up (see below); their

Table 1. Characteristics of patients at randomization

	Early treatment (n = 78)	Control (n = 77)
Age (years)	26·1 (7)	25·9 (6)
Mean weight at 20th week (kg)	71·9 (12)	74·2 (17)
Height (cm)	164 (5)	163 (6)
Primiparous	30 (39)	36 (47)
Hypertension in previous pregnancy*	18 (38)	12 (29)
Previous perinatal death*	3 (6)	5 (12)
Previous small-for-dates baby*	7 (15)	7 (17)
Proteinuria at entry >1+	2 (3)	4 (5)
Gestation at entry (weeks)	28·0 (5)	28·2 (5)
Sitting blood pressure (mmHg)	142/91 (9/6)	143/91 (10/7)

Results are means (SD) and n (%) as appropriate.

* In parous women.

records are included in the analysis of the results. Mean follow-up from entry to delivery was similar in the two groups: 10·3 weeks (SD 6) in the early treatment group and 9·6 (SD 6) in the control group with an average of 5·5 visits in both groups.

Mean BP after entry was lower in the early treatment group than in the control group, and the difference was statistically significant at the 2nd week after allocation to double-blind treatment (Table 2). Open, active treatment was required because of failure to control BP in five women in the early treatment group and in 11 in the control group. Consequently, there was no significant difference in the mean BP between the two groups at the last prenatal outpatient visit (141/88 mmHg, SD 21/14, *vs* 144/89, SD 19/15). Four women in the early treatment group and three in the control group were withdrawn from blind treatment for side-effects, poor compliance, or both. Neither the mean plasma urate concentration nor the frequency of significant proteinuria differed significantly between the two groups (Table 2). The number admitted to hospital before delivery and the mean duration of prenatal admissions were also similar in the two groups.

Delivery data

Gestation at delivery did not differ significantly between the two groups but important differences were found in the mode of delivery (Table 3). Spontaneous labour was more frequent in the early treatment group, while induction of labour and elective caesarean section before labour tended to be more frequent in the control group (d.f.=2, P=0·03). The number of caesarean sections in the early treatment group was half that in the control group (13 *vs* 27, 95% CI of difference: 5–33%, P<0·01). The reduced frequency of caesarean section in the early treatment group was still present after exclusion of those whose treatment had been unblinded before the decision to perform section (20 of 65 *vs* 11 of 67, or 16 *vs* 31%, P=0·05). This reduction was significant for primiparae (early treatment group: 4 of 30, control group: 13 of 36, P=0·04), in women who had had a DBP above 94 mmHg at entry (early treatment group: 5 of 30, control group: 13 of 30, P=0·02), and in those included at a gestational age of 26–35 weeks (early treat-

Table 2. Maternal outcome

	Early treatment (n = 78)	Control (n = 76)
Blood pressure 2 weeks after entry		
Systolic (mmHg)	131 (6)	137 (17)
Diastolic (mmHg)	82 (14)	84 (13)
Treatment at delivery		
Double-blind, steps 1/2*	60 (76)	48 (64)
Double-blind, steps 3/4†	9 (12)	14 (18)
Withdrawn from blind treatment	9 (12)	14 (18)
Reasons for withdrawal		
Diastolic pressure >105 mmHg	5 (6)	11 (14)
Poor compliance/side-effects	4 (5)	3 (4)
Proteinuria >1+	7 (9)	7 (9)
Plasma urate (µmol/l)		
Maximum level	327 (97)	318 (103)
No. with levels ≥360	23 (30)	20 (27)
Admission before delivery	48 (61)	46 (60)
Days in hospital	7 (10)	9 (11)

Results are means (SD) and n (%) as appropriate. The only significant difference between the two groups was in blood pressure levels: P<0·001 for systolic and P<0·05 for diastolic pressures (unpaired t-test).

* Steps 1 and 2: 160 and 320 mg/day oxprenolol or matching placebo.

† Steps 3 and 4: 320 mg/day oxprenolol + 50 mg/day dihydralazine and 320 mg/day oxprenolol + 100 mg/day dihydralazine or matching placebo

Table 3. Labour and delivery

	Early treatment (n = 78)	Control (n = 76)	95% CI
Gestational age (weeks)	38·4 (2)	38·1 (3)	−1·0 to 0·4
Onset of labour			
Spontaneous	54 (70)	38 (50)	
Induced	12 (15)	24 (32)	
Caesarean sections (CS)			
Elective before labour	12 (15)	14 (18)	
Total no.	13 (17)	27 (36)	5 to 33%*
For fetal distress or severe hypertension	7 (9)	16 (21)	
Induced labour or CS for fetal distress and/or severe hypertension	11 (14)	24 (32)	5 to 31%*
Postnatal hospitalization (days)	6·2 (2·3)	7·7 (3·3)	0·5 to 2·4*

Results are means (SD) and n (%) as appropriate.
CI, Confidence intervals of differences between groups (control minus early treatment).
* Significant differences between the groups (t- or χ^2-tests as appropriate).

ment group: 8 of 54, control group: 20 of 50, $P<0\cdot01$), but it was not statistically significant in multiparae, in patients with a DBP below 95 mmHg at entry, or in those who entered the trial before the 26th week of pregnancy. Fetal distress detected by fetal heart-rate monitoring, generally associated with acute worsening of hypertension (that is, rapid increase in DBP, proteinuria, or both, or symptoms of impending eclampsia), led to induction of labour or caesarean section in 24 women in the control group and 11 in the early treatment group (32 *vs* 14%, 95% CI of difference: 5–31%, $P<0\cdot01$). The mean duration of postnatal maternal stay in hospital was slightly but statistically significantly longer in the control group.

No eclampsia occurred in either group. One woman allocated to early treatment died during caesarean section. This patient was included during the 25th week of her ninth pregnancy on

Table 4. Summary of perinatal deaths

Gestation (weeks)	Birthweight (g)	Proteinuria	Highest diastolic (mmHg)	Treatment at		Remarks
				Random -ization	Delivery	
Stillbirths						
31	780	0	80	Active	Step 1 (17)	Induced labour for fetal death
24	400	2+	90	Active	Step 1 (1)	Placental abruption, spontaneous labour
25	400	4+	120	Placebo	Open active, step 6 (8 + 26)	Induced labour for fetal death
Neonatal deaths						
31	1200	3+	140	Placebo	Open i.v. hydralazine (9 + 2)	CS before labour for severe pre-eclampsia, death at day 5
34	1800	2+	100	Placebo	Placebo, step 4 (8)	CS before labour for fetal distress, multiple malformations, death at day 4

The number in parentheses denotes days of treatment from inclusion to delivery.
Step 6: 320 mg/day oxprenolol + 100 mg/day hydralazine + 1 g/day methyldopa.
CS, Caesarean section.

Table 5. Perinatal outcome for liveborn babies

	Early treatment (n = 76)	Control (n = 75)	95% CI
Mean birthweight (g)			
All babies	3079 (496)	3023 (693)	−248 to 136
By gestation (weeks)			
31–34	1950 (n = 1)	1650 (n = 5)	
35–36	2619 (n = 8)	2560 (n = 8)	
>36	3151 (n = 67)	3193 (n = 62)	
No with IUGR	5 (7)	8 (11)	
Blood glucose at birth (mmol/l)	4·3 (1·3)	4·1 (2·3)	
No. with Apgar score <7 at 1 min	8 (11)	16 (21)	
at 5 min	3 (4)	2 (3)	
No. transferred to neonatal unit	16 (21)	24 (32)	−1 to 27%
No transferred for respiratory distress syndrome	4 (5)	10 (13)	
Neonatal deaths	0	2	
No. of surviving babies in hospital for >10 days	14 (18)	26 (36)	4 to 32%*

Results are means (SD) and n (%) as appropriate.
IUGR, Intrauterine growth retardation
* $P<0\cdot01$ (χ^2-test).

the basis of a BP of 140/100 mmHg with no proteinuria. Her BP was unchanged at a visit during the 27th week but she was then considered to be complying with treatment. She later abandoned treatment and visits and was seen at home by a midwife. At the 34th week, her BP was 160/120 mmHg but she refused admission to hospital until the 36th week, when her BP was 220/150 mmHg and she had a 4+ proteinuria dip-test. Caesarean section was performed after a few hours of labetalol infusion, resulting in the birth of a healthy boy weighing 2300 g who survived.

Perinatal outcome

The perinatal deaths are detailed in Table 4. Two stillbirths occurred in women who had been allocated to early treatment and had had adequate BP control; in one stillbirth the cause was unknown and the other was due to placental abruption which occurred the day after inclusion. One fetal and one neonatal death occurred in the control group after severe pre-eclampsia; both women had been changed to active, open treatment because of a DBP above 105 mmHg and proteinuria A preterm infant born to a third woman in the control group died at day 4 because of multiple malformations.

In the liveborn babies, mean birthweight and birthweight distribution by gestation were similar in the two groups (Table 5), as was the mean blood glucose level at birth. Infants who had a low Apgar score at 1 min or were transferred to a neonatal unit were fewer in the early treatment than in the control group; respiratory distress syndrome was the reason for the transfer of four infants in the early treatment group and 10 in the control group. Finally, half as many surviving infants in the early treatment group stayed in hospital for more than 10 days in a neonatal unit as in the control group (18 *vs* 36%, 95% CI of difference: 4–32%, $P=0\cdot03$).

Discussion

In the present trial, mean BP was lower in the early treatment group than in the control group during the weeks following inclusion but the difference eventually decreased because those women in the control group whose DBP rose above 105 mmHg were given active treatment. Unlike the results reported by Rubin *et al.* (1983), treatment allocation did not affect either the evolution of proteinuria when it was present at entry, or the occurrence of subsequent proteinuria. The mean gestation at delivery was identical in the two groups and the slight difference in birthweight was neither clinically nor statistically significant. This negative finding may imply that in PIH, either IUGR is not dependent on BP or it cannot be reversed by pharmacological reduction of the BP. Another possibility is that the expected benefit for fetal growth due to a reduction in BP was obscured by the small transient intergroup difference in BP. Birthweight was normal in most of the infants in the control group and so was the prenatal BP of their mothers because of the antihypertensive effects of placebo, home rest, diet counselling and hospital admission, and the availability of active treatment when hypertension was severe.

Although in terms of fetal growth early antihypertensive treatment had no advantage over non-pharmacological care plus drug restriction to severe cases, it nevertheless led to large intergroup differences in the mode of delivery and to an improvement in pregnancy outcome. Thus, in the early treatment group, the numbers of caesarean sections and of infants with respiratory distress syndrome severe enough to require transfer to a neonatal unit were smaller than in the control group. Consequently, the number of surviving babies needing to stay for more than 10 days in a neonatal unit in the early treatment group was half that in the control group. The rate of caesarean section, the proportion of infants transferred to a neonatal unit, and the length of neonatal stay are interdependent, as delivery by caesarean section might increase the risk of neonatal respiratory distress (Faxelius *et al.* 1983). It is therefore important to examine whether treatment allocation influenced the pattern of medical intervention in the present trial. Differences in this pattern cannot be ascribed to knowledge of treatment, since our trial was double-blind. Earlier obstetric intervention in the control group because of poor BP control is unlikely to have been important since gestation at delivery did not differ between the two groups. However, the fact that the mean BP levels recorded at the last outpatient visit were similar in the two groups does not rule out the possibility that the antihypertensive effect of treatment affected the outcome, because severe or proteinuric hypertension, generally associated with acute fetal distress, was the primary indication for labour induction or caesarean section in 14% of the patients in the early treatment group compared with 32% in the control group. Early treatment may have prevented the acute worsening of PIH/pre-eclampsia in the last days or hours of pregnancy and so lessened the frequency of associated fetal distress. This would lead to a reduction in the frequencies of caesarean section, respiratory distress syndrome and prolonged neonatal admissions. However, it should be noted that these are hypotheses generated by the results of our trial and these effects of early treatment in pregnancies complicated by PIH need to be studied prospectively.

The present findings, combined with the results of the trials reported by Rubin *et al.* (1983), and more recently by Pickles *et al.* (1989), favour early administration of oxprenolol, atenolol or labetalol in mild to moderate PIH and these beta-blockers appear to be safe for the fetus and the newborn (Rubin *et al.* 1983; Gallery *et al.* 1979; Fidler *et al.* 1983; Plouin *et al.* 1988).

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Doppler umbilical and uterine flow waveforms in severe pregnancy hypertension

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Summary. Doppler studies of the umbilical and uteroplacental bed arterial flow velocity waveforms were performed in a series of women suffering from severe proteinuric pregnancy hypertension. Ninety-five women were studied and the mean interval between the last study and delivery was 1·4 days. An abnormally elevated umbilical artery systolic-:diastolic (AB) ratio was present in 61 (64%) of the women. All 10 perinatal deaths were associated with pregnancies with an abnormal umbilical artery AB ratio. An elevated umbilical artery AB ratio was significantly associated with small-for-gestation and neonatal morbidity. Infants associated with extremely high umbilical artery AB ratios (⩾ 99th centile) spent twice as long in the neonatal nursery as those with a lower value. There was no relation between the duration of hypertension and the umbilical study result. The uteroplacental bed artery flow velocity waveform did not correlate with fetal or neonatal mortality or morbidity. Patients with abnormal uteroplacental AB ratios also had abnormal umbilical artery AB ratios. We conclude that an abnormal fetal umbilical artery Doppler flow velocity waveform correlates with adverse fetal outcome in severe proteinuric pregnancy hypertension and suggest that the associated placental lesion may precede the maternal hypertension.

Doppler studies of flow velocity waveforms may be performed to assess both the fetal umbilical and maternal uterine circulations. The two common pregnancy complications associated with abnormality of the umbilical artery flow velocity waveform are fetal growth retardation and maternal hypertension (Trudinger *et al.* 1985; Fleischer *et al.* 1985; Erskine & Ritchie 1985; Reuwer *et al.* 1984). Umbilical Doppler studies have been shown to be of value in the management of high fetal risk pregnancies (Trudinger *et al.* 1987), but the usefulness of uterine artery Doppler studies is controversial. Abnormality of the uterine artery flow velocity waveforms has variously been reported to precede maternal hypertension (Campbell *et al.* 1986; Steele *et al.* 1988), to be associated with more severe degrees of hypertension (Fleischer *et al.* 1986), and to be inconsistently associated with hypertension (Hanretty *et al.* 1988). Current teaching associates maternal hypertension with inadequate uteroplacental blood flow, and consequent deprivation of the fetus. Doppler studies would seem well suited to demonstrate this. In the present study we report the results of Doppler studies of the maternal and fetal placental circulations in a large group of women with severe proteinuric pregnancy hypertension. The purpose of this study was to record the umbilical

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and uterine flow velocity waveforms in severe hypertensive disease of pregnancy and to relate these findings to the severity of the maternal disease and fetal outcome. Since hypertension in pregnancy entails maternal and fetal risk factors, a correlation between Doppler findings and clinical outcome may permit formulation of management strategies incorporating this information.

Patients and methods

The study included 95 patients with severe proteinuric pregnancy hypertension defined as a diastolic blood pressure ≥110 mmHg on two occasions >24 h apart with proteinuria > 1g/24h. Information about the gestational age at which the diastolic blood pressure measured ≥90 mmHg and the duration of hypertension was obtained from the antenatal records. The maternal plasma urate was used as a marker of renal involvement and the highest value noted. The last antepartum maternal platelet count was also noted. Fetal outcome was recorded in terms of birthweight and centile weight (Kitchen *et al.* 1983), Apgar scores at 1 and 5 min, admission and duration of stay in the neonatal intensive care (Level III) nursery. For each infant a growth failure duration deficit was calculated as the number of days from the observed birthweight against gestation to the gestation at which the same birthweight was the 50th centile value. This interval was calculated to provide an index of the severity and duration of growth failure.

Umbilical artery Doppler flow velocity waveforms were studied as described previously by Trudinger *et al.* (1985*a*). The 95th and 99th centile values were calculated from our normal range (Thompson *et al.* 1988). A systolic: diastolic (AB) ratio above the 95th centile but below the 99th centile was classed as high, and a value ≥99th centile was classed as extreme. Uterine artery flow velocity waveforms were recorded from branches in the placental bed (Trudinger *et al.* 1985*b*). An AB ratio ≤95th centile was classified as normal and high if above this.

The reason for the Doppler study was maternal hypertension and in general measurements were made at weekly intervals after the maternal blood pressure had been noted to be elevated. Since it was unit policy to investigate with Doppler all women with severe pregnancy hypertension there were no selection biases in this group.

Statistical differences between groups were determined using either a *t*-test or the χ^2-test for categorical data. A level of 0·05 was required for significance.

Results

Of the 95 patients included in this study 69 were primigravidae. The mean maternal age was 25 years (SD 5, range 15–39). The mean gestational age at the time of the first Doppler study was 31·7 (SD 4·4) weeks and 32·9 (SD 3·5) weeks at delivery. The mean birthweight was 1674 (SD 779)g. The birthweight of 31 infants was <10th centile and 18 infants had a birthweight between the 10th and 25th centiles.

A Doppler umbilical artery flow velocity waveform recording was available for all patients within 7 days of delivery. The mean interval between the last study and delivery was 1·4 (SD 1·9) days (interquartile range 0 to 2). The AB ratio of the last study for each patient is shown in Fig. 1 and details of the pregnancies are shown in Table 1. There were 10 perinatal deaths, eight of the infants were born before 30 weeks and the other two were born at 32 and 34 weeks, both had a major fetal abnormality. Two of the 10 perinatal deaths were associated with high umbilical artery AB ratios and the other eight with extreme AB ratios. The number of small-for-gestational-age (SGA) infants, the fetal growth failure duration deficit, and the duration of stay of newborns in the Level III nursery were greatest in the group with an extreme umbilical artery AB ratio. The neonatal data were examined in gestational age blocks to eliminate bias resulting from preterm births. Maternal platelet counts and uric acid levels were examined. In 87 of the 95 women a platelet count result was available. Significantly more women with an extreme umbilical artery AB ratio had a count $<150\times10^6$/l in comparison to women with a normal or high AB ratio. There was no difference between groups in the maternal plasma uric acid level.

The uterine artery flow velocity waveform recorded from the placental bed was available in the first 37 women (Table 2). The mean interval between the last study and delivery was 1·6 (SD 1·9) days. The AB ratios are shown in Fig. 2a. There were no significant differences in outcome between the normal and high AB ratio groups apart from the maternal platelet count.

The last umbilical and uteroplacental artery

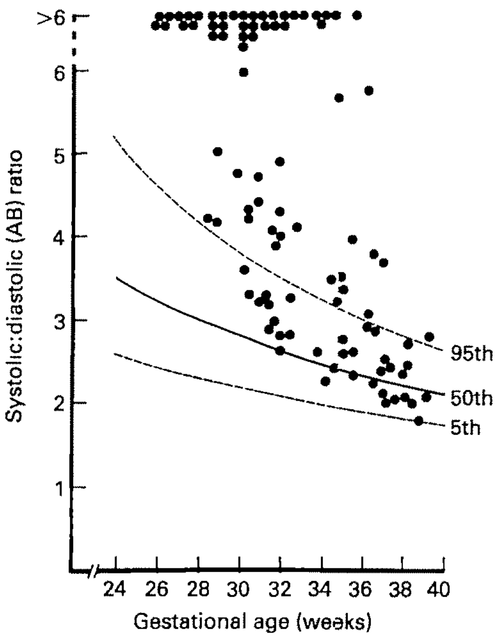

Fig. 1. The last study umbilical artery systolic:diastolic (AB) ratio plotted against the gestational age at the time of this study shown against 5th, 50th and 95th centiles calculated from the normal range (Thompson *et al.* 1988).

flow velocity waveforms were compared in the 37 pregnancies where this information was available (Fig. 2a & b). The most abnormal uterine waveforms (Fig. 2a) were associated with an abnormal umbilical waveform. No such relation was apparent when the abnormal umbilical artery AB ratios were considered. Of the 26 women with an abnormal umbilical AB ratio 10 (38%) had an abnormal uterine artery AB ratio, whereas of the 11 pregnancies with a normal umbilical AB ratio, 3 (27%) had an abnormal uterine artery AB ratio. These results indicate that although an abnormal uteroplacental AB ratio (>95th centile) is associated with an abnormal umbilical AB ratio, an abnormal umbilical AB ratio is not necessarily associated with an abnormal uteroplacental artery AB ratio.

Adequate antenatal records were available for 71 patients to assess the duration of hypertension. When the patients were dichotomized according to the last umbilical artery AB ratio, normal (<95th centile) or abnormal (≥95th centile), the mean duration of hypertension was 21·8 and 26·1 days in these two groups respectively; this difference is not statistically significant. When the patients were dichotomized according to the result of the last uterine artery AB ratio, there was a significant difference in the

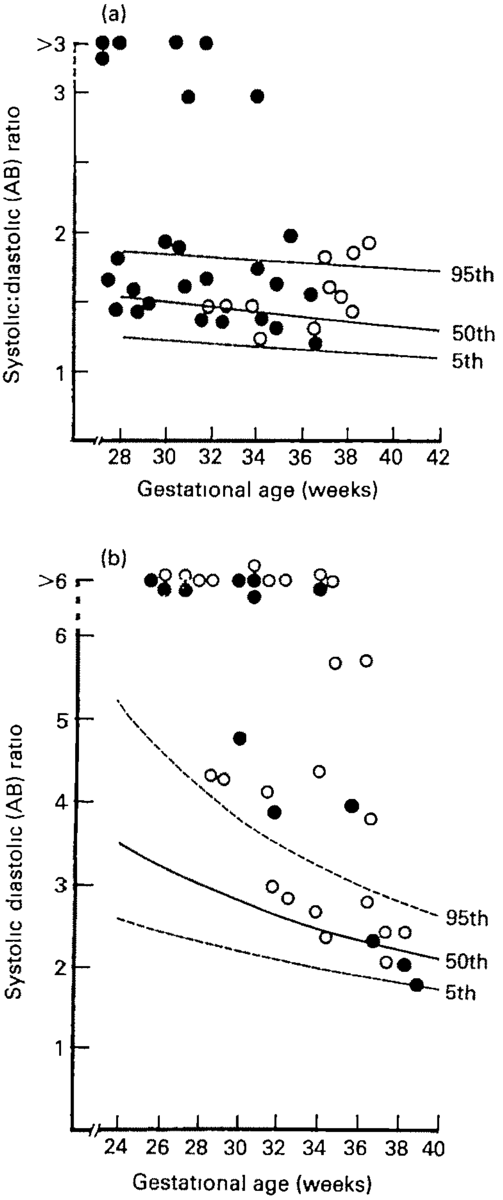

Fig. 2. (a) The last study uteroplacental bed artery systolic:diastolic (AB) ratio plotted against gestational age according to whether the last umbilical artery flow waveform AB ratio was normal (○) or abnormal (●). (b) The last study umbilical artery systolic:diastolic (AB) ratio plotted against gestational age according to whether the last uteroplacental bed flow waveform AB ratio was normal (○) or abnormal (●) Centiles calculated from the normal range (Thompson *et al.* 1988).

Table 1. Outcome in relation to the last umbilical artery Doppler flow velocity waveform AB ratio

	Umbilical artery AB ratio centile		
	Normal (<95th)	High (>95th, <99th)	Extreme (≥99th)
Total no. of pregnancies	34	12	49
Gestation at delivery (weeks)			
Mean (SD)	35·3 (2·9)	33·0 (3·2)	31·2 (2·9)***
No. of perinatal deaths	0	2	8**
Birthweight (g)			
Mean (SD)	2274 (782)	1706 (696)	1249 (467)***
No. with birthweight <10th centile	7	4	20*
Growth failure duration deficit (days)			
Mean (SD)	6·5 (14·4)	10·5 (10·9)	16·5 (10·9)***
No. with Apgar score ≤6 at			
1 min	6 (18%)	7 (64%)	34 (69%)***
5 min	6 (18%)	1 (9%)	10 (20%)
No. admitted to NICU	18	9	47***
Duration of stay in NICU >10 days			
(no. of babies)	7	5	33*
Mean days (no. of babies)			
Gest. del. 30–32 weeks	27·1 (10)	14·8 (4)	43·5 (19)*
Gest. del. 33–36 weeks	7·2 (5)	17·0 (1)	19·7 (9)
Gest. del. >36 weeks	3·0 (3)	3·0 (2)	7·7 (3)
Maternal studies			
Platelet count <150 × 10⁶/l	5/29 (17%)	2/11 (18%)	18/47 (38%)*
Plasma urate >500 μmol/l	9/28 (32%)	6/11 (55%)	13/44 (30%)

NICU, Neonatal intensive care unit; Gest. del., gestation at delivery
Significantly different from group with normal umbilical artery AB ratios: * $P<0{\cdot}05$, ** $P<0{\cdot}01$; *** $P<0{\cdot}001$.

mean duration of hypertension between the two groups, 8·5 days in the group with normal AB ratios and 45·7 days in the group with abnormal AB ratio.

Discussion

Severe proteinuric pregnancy hypertension is associated with abnormality of the fetal umbilical artery flow velocity waveform. Two-thirds of women referred for study because of the hypertension exhibited a high or extreme AB ratio. This finding confirms our observation in a smaller group of severely hypertensive women (Trudinger *et al.* 1985*c*) and the findings amongst the more severely affected of a less selected group with hypertension (Ducey *et al.* 1987). Unlike previous studies our present report was restricted to women with severe proteinuric hypertension to ensure a group in whom the diagnosis of pre-eclampsia was certain. We have demonstrated that in severe proteinuric hypertension poor fetal outcome in terms of perinatal mortality, small-for-gestation and need for neonatal intensive care correlate with the degree of abnormality of the umbilical artery AB ratio. No such correlation was apparent for either duration of hypertension or uric acid level (renal function) as markers of severity of the maternal hypertension. Abnormality of the maternal uteroplacental artery flow velocity waveform was inconsistent and did not correlate with fetal outcome. Our findings in relation to the uteroplacental artery AB ratios disagree with reports relating abnormality in the uteroplacental artery waveform to severity of the fetal effect.

There is uncertainty about the changes in the uteroplacental Doppler waveform in pregnancy hypertension. Although it has been reported to be abnormal in pregnancy hypertension (Trudinger *et al.* 1985*b*), not all authors (Hanretty *et al.* 1988) support the observation that the degree of abnormality is related to the severity of the hypertension (Fleischer *et al.* 1986). In the present study we found that many women with severe hypertension had normal uteroplacental artery flow velocity waveforms. This finding does not support the possible use of utero-

Table 2. Outcome in relation to last uteroplacental artery flow velocity waveform AB ratio

	Uteroplacental artery AB ratio centile	
	Normal (<95th)	High (≥95th)
Total no. of pregnancies	24	13
Gestational age at delivery (weeks)		
Mean (SD)	33·1 (3·5)	32·1 (4·3)
No. of perinatal deaths	3	1
Birthweight (g)		
Mean (SD)	1710 (735)	1560 (854)
No. with birthweight <10th centile	8	5
Growth failure duration deficit (days)		
Mean (SD)	11·9 (13·5)	12·6 (10·8)
Admission to NICU		
Total no. of babies	21	9
No staying >10 days	9	7
Maternal studies		
Platelet count <150 × 10^6/l	4/23 (17%)	5/12 (42%)*
Plasma urate >500 μmol/l	8/24 (33%)	2/10 (20%)

NICU, Neonatal intensive care unit

Significantly different from group with normal uteroplacental artery AB ratios: *$P<0·05$.

placental waveforms to predict pre-eclampsia (Campbell *et al.* 1986; Steele *et al.* 1988). In part this conflict may result from recordings from different vessels (Pearce & McParland 1988; Campbell *et al.* 1988). Our technique selects for study, arcuate or radial branches of the uterine artery in the placental bed. Some authors have used our method whilst others have attempted to study the main uterine trunk. The poor reproducibility of all these studies has been noted. Although the flow pattern in any individual radial placental bed channel may be normal, recordings from the main uterine trunk could be expected to reflect the number of such channels. In the presence of a poor placental stimulus to uteroplacental vascularization, the number of channels and so the extent of the placental bed will be reduced and thus a high resistance pattern uterine waveform may be recorded. In those patients in whom the uteroplacental bed flow velocity waveform is abnormal, we have suggested there is vascular disease in the small arterial vessels of the placental bed (Trudinger *et al.* 1985*c*). The longer duration of the hypertension in patients with an abnormal uteroplacental study in the present work is consistent with pre-existing vascular disease in the placental bed in this group.

Pre-eclampsia is widely regarded as associated with uteroplacental ischaemia and many believe that this constrains the fetus. Our results do not support this sequence. There was no correlation between the duration of hypertension or maternal plasma uric acid level and the degree of effect on the umbilical placental circulation. Abnormal umbilical Doppler studies are associated with a pathology in the umbilical placental vasculature (Giles *et al.* 1985). To explain our findings, we speculate that the development of the placental vascular lesion, which deprives the fetus, is the primary vascular pathology, and the manifestation of hypertension in the mother is secondary to this, occurring if the mother is susceptible in some way. Since the umbilical and uterine placental circulations are in balance, a restriction on the umbilical side will be associated with a reduced requirement for uterine blood flow. This hypothesis of a fetal placental vascular origin for hypertension does not explain the occurrence of hypertension in association with normal umbilical Doppler studies. However, using a mathematical model of the placental circulation we have examined the theoretical basis of the umbilical Doppler study (Thompson & Trudinger 1990). This model predicts that it is necessary to obliterate approximately 60% of the umbilical placental vascular bed before the Doppler study moves beyond the normal range. It is thus possible for very susceptible women to manifest hypertension before the extent of umbilical obliteration has reached this level. We have also demonstrated that normotensive women with abnormal fetal umbilical artery Doppler studies (and subsequent fetal morbidity) are angiotensin sensitive (Trudinger & Cook 1989) in the same manner as demonstrated for those destined to develop pre-eclampsia (Gant *et al.* 1973). The beneficial effects of aspirin in preventing the occurrence of hypertension (Beaufils *et al.* 1983; Wallenburg *et al.* 1986) have been attributed to a block in the release of vasoconstricting prostaglandins, otherwise responsible for angiotensin sensitivity and hypertension. However, in normotensive women with an abnormal umbilical Doppler study we have shown that low-dose aspirin increases placental and fetal weight and, by inference, stops the placental pathology (Trudinger *et al.* 1988). If the umbilical Doppler identifiable placental lesion precedes both fetal constraint and maternal hypertension, then our observations would explain the beneficial effects of aspirin for both mother and fetus.

The principles of management of pregnancy hypertension are simple. Delivery is the definitive treatment. If maternal condition can be safeguarded then delivery may be deferred in order to allow fetal growth and maturity. Powerful hypotensive therapy is available. Since Doppler umbilical studies predict fetal condition then it would be reasonable to use such studies to determine those patients suitable for conservative therapy aimed at gaining further fetal maturity before delivery.

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Progestogen administration in pregnancy may prevent preterm delivery

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Summary. Two recently published meta-analyses of controlled trials of a wide variety of progestational agents, used in pregnancy (Daya 1989; Goldstein *et al.* 1989), prompted this third meta-analysis of placebo-controlled trials involving the prophylactic use of a single agent, 17α-hydroxyprogesterone caproate. Of seven relevant published reports of controlled trials, six had involved women considered to be at high risk of miscarriage or preterm birth. This analysis provides no support for the view that 17α-hydroxyprogesterone caproate protects against miscarriage, but suggests that it does reduce the occurrence of preterm birth. The latter effect was reflected in a reduced rate of low birthweight babies, but not in a statistically significant reduction in perinatal mortality and morbidity. The difference between this meta-analysis and the two earlier meta-analyses illustrates the problems both of selective subgrouping and of comprehensive pooling of data from small trials.

A communication by Allen *et al.* (1935) reported their agreement to use henceforth only the name progesterone for the pregnancy-maintaining hormone extracted from corpora lutea previously known as luteosteron and progestin. Their communication appeared on the same page that introduced 'prostaglandin' for the first time (von Euler 1935). It was not to be anticipated, however, that 50 years later there would be wide consensus on the effects of prostaglandin administration, but not on the effects of progesterone administration in pregnancy.

Recently, Daya (1989) and Goldstein *et al.* (1989) reported separate meta-analyses assessing the effects of progestogen administration in pregnancy, but reached contradictory conclusions. Daya (1989) concluded that the available evidence supported a beneficial effect on the risk of early pregnancy failure, whereas Goldstein *et al.* (1989) concluded that the data did not support such a conclusion.

One may be inclined to attribute this difference in opinion to semantics: Daya (1989) reported on 'progesterone'; whereas Goldstein *et al.* (1989) reported on 'progestational agents'. This is not so, however. Only one of the three studies included by Daya (1989), the trial of Swyer and Daley (1953), actually used progesterone. Daya's conclusions are thus based on as wide an array of agents as those of Goldstein *et al.* (1989).

Because there are large differences among the many agents considered to be progestational on the basis of pharmacological tests, I have conducted a third, more restricted meta-analysis using data from all placebo-controlled trials involving prophylactic use of the most fully studied progestational agent, 17α-hydroxyprogesterone caproate.

Materials and methods

Placebo-controlled trials of 17α-hydroxyproges-

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terone caproate used alone were identified using the Oxford Database of Perinatal Trials (Chalmers 1988) and the reference lists of Daya (1989) and Goldstein *et al.* (1989).

Of nine trials that appeared eligible for inclusion two were excluded. One was excluded (Goldzieher 1964) because the introduction to the report stated that hydroxyprogesterone caproate had been used, while the Summary and Results referred to medroxyprogesterone acetate. The study was listed as a hydroxyprogesterone caproate trial by Daya (1989) and as a medroxyprogesterone acetate trial by Goldstein *et al.* (1989), but it was sponsored by the Upjohn Company, which manufactures the latter agent. The other trial (Tognoni *et al.* 1980), which had used more than one active agent, was excluded because it was impossible to identify separately the women who had received 17α-hydroxprogesterone caproate.

The characteristics of the seven remaining trials, including the type of women who participated in the studies, the doses and duration of treatment, and the outcomes that were available for study are shown in Table 1. All except one (Shearman 1968) of these trials had been included in the meta-analysis of Goldstein *et al.* (1989), but only one (LeVine 1964) was included by Daya (1989). The quality of the trials was assessed with the method described by Chalmers *et al.* (1989); all trials were reported to have been conducted in a double-blind manner.

Outcome measures sought were: first, early curtailment of gestation whether by miscarriage (<20 weeks or <500 g; FIGO News 1976; World Health Organization 1977) or by preterm birth (<37 weeks; FIGO News 1976; World Health Organization 1977); second, any available data on the mechanisms by which these outcomes might be achieved, such as preterm labour or prelabour rupture of the membranes; and, third, outcomes that might reflect the consequences of early delivery for the infant, such as perinatal death.

The effects of prophylactic drug *versus* placebo treatment for each of the outcomes available from the reports was expressed as the ratio with the 95% confidence intervals (CI) between the odds of an adverse outcome in the actively treated group and the odds of an adverse outcome in the placebo group. All of the trials individually were too small to have reasonable power to detect clinically important differences in outcome. The differences between active and placebo treatment from each individual study were combined to yield a 'typical' odds ratio across trials with the method described by Yusuf *et al.* (1985); its mathematical details have been described by Chalmers *et al.* (1989).

Results

Data on miscarriage were available from only four of the seven trials; three of these four trials were included by Goldstein *et al.* (1989), but only one in the analysis of Daya (1989). None of the trials individually showed a statistically significant effect of the active drug, but they were all too small to have reasonable power to detect such an effect. Even the typical odds ratio across trials refers to only 104 actively treated women; its 95% CI (0·61 to 2·74, which includes unity) provides no suggestion of a beneficial effect on the likelihood of miscarriage (Table 2).

Five of the seven trials provided data on preterm birth. In all but one of these trials (Hartikainen-Sorri *et al.* 1980; the only trial dealing with twin pregnancies) there were fewer preterm deliveries in actively treated than in placebo-treated women; the 95% CI (0·30 to 0·85) of the typical odds ratio indicated a statistically significant reduction in the frequency of preterm birth with the active treatment (Table 2). There was also a significant reduction in the frequency of preterm labour (but not in the frequency of prelabour rupture of the membranes) although data on these outcomes were each available from only two of the five trials (Table 2).

The lower frequency of preterm birth was reflected in a statistically significant reduction of the number of low-birthweight infants (Table 2). The lower frequency of preterm birth and of low birthweight did not result in a statistically significant reduction in perinatal mortality, nor in the occurrence of the two measures of infant morbidity (respiratory distress syndrome and hyperbilirubinaemia) that were available for analysis; the 95% CI of these typical odds ratios all included unity (Table 2).

The typical odds ratios and 95% CI across trials for the various outcomes are depicted graphically in Fig. 1. The figure demonstrates that all of the confidence intervals—irrespective of whether or not they reach the conventional level of statistical significance ($P<0·05$)—are wide. This implies that the confidence intervals, which do not reach statistical significance, may hide effects that

Table 1. Characteristics of placebo controlled trials of 17α-hydroxyprogesterone caproate

		Treatment characteristics			No. treated: reported		
Authors*	Entry criteria	Dose	Started	Stopped	Active drug	Placebo	Data on outcomes†
LeVine (1964)	History ≥3 miscarriages	500 mg weekly	Booking at <16 weeks	36 weeks	— 56 entered — ?:15	?:15‡	1, 4, 5, 6
Shearman (1968)	History ≥2 miscarriages + low urine pregnanediol	250 mg weekly	At booking	24 weeks	27:27	23:23	1
Papiernik-Berkhauer (1970)§	High preterm risk score	250 mg every 3 days (8 doses)	28–32 weeks	After 8 doses	50:50	49:49	4, 5, 6
Johnson *et al.* (1975)	History ≥2 miscarriages/ preterm births	250 mg weekly	At booking	37 weeks	23:18	27:25	1, 4, 5, 6
Hartikainen-Sorri *et al.* (1980)	Twin pregnancy	250 mg weekly	28–33 weeks	37 weeks	39:39	38:38	2, 4, 6, 7, 8
Hauth *et al* (1983)	Non-selected women (active duty military personnel)	1000 mg weekly	16–20 weeks	36 weeks	80·80	88:88	3, 5, 6
Yemini *et al.* (1985)	History ≥2 miscarriages/ preterm births + viable fetus on ultrasound	250 mg weekly	At booking	37 weeks	40:39	40:40	1, 2, 3, 4, 5, 6, 7, 8
			(all women also had cervical sutures inserted)				

* All trials except that of Shearman (1968) were included in the meta-analysis of Goldstein *et al* (1989), only the trial of LeVine (1964) was included in the meta-analysis of Daya (1989).

† 1, Miscarriage; 2, prelabour rupture of membranes; 3, preterm labour; 4, preterm birth; 5, birthweight <2500 g; 6, perinatal death excluding malformations; 7, respiratory distress; 8, hyperbilirubinaemia.

‡ Includes one case allocated to placebo, excluded by Goldstein *et al* (1989).

§ Denominators include all women entered into the trial.

could be present and that, if present, would be clinically important.

Discussion

The results of this meta-analysis of placebo-controlled trials of a single progestational agent do not support the tentative conclusion of a beneficial effect of 'progesterone' on the occurrence of miscarriage as suggested by Daya (1989). It should be noted that all women included in this part of my meta-analysis were reported to have had at least two previous pregnancies ending in miscarriage or preterm birth (Table 1). Of the four trials that provided data on miscarriage, only the one with the most favourable results of treatment (LeVine 1964) had been included by Daya (1989). It cannot be denied that Daya (1989) applied more stringent selection criteria, but it is relevant that his three selected studies scored low on the quality assessment of Goldstein *et al.* (1989) and that they included a 'trial' (Goldzieher 1964) that failed to indicate unequivocally what agent had been administered.

It is worth emphasizing that the analysis of Daya (1989) was based on a 'selective' selection of only 50 actively treated women of whom not more than 27 actually received progesterone. It

Table 2. Effects of 17α-hydroxyprogesterone caproate administration in pregnancy on various pregnancy outcomes

Pregnancy outcome and study	17α-hydroxy-progesterone	Placebo	Odds ratio (95% CI)
Miscarriage			
Shearman (1968)	5/27	5/23	0·82 (0·21– 3·25)
Yemini *et al.* (1985)	8/39	3/40	2·92 (0·82–10·36)
LeVine (1964)	3/15	7/15	0·31 (0·07– 1·39)
Johnson *et al.* (1975)*	3/23	0/27	9·64 (0·95–97·98)
Typical odds ratio			1·30 (0·61– 2·74)
Prelabour rupture of membranes			
Hartikainen-Sorri *et al.* (1980)	5/39	2/38	2·47 (0·53–11·55)
Yemini *et al.* (1985)	2/39	3/40	0·67 (0·11– 4·08)
Typical odds ratio			1·42 (0·44– 4·59)
Preterm labour			
Hauth *et al.* (1983)	5/80	5/88	1·11 (0·31– 3·96)
Yemini *et al.* (1985)	9/39	22/40	0·27 (0·11– 0·65)
Typical odds ratio			0·43 (0·20– 0·89)
Preterm birth			
Papiernik-Berkhauer (1970)†	2/50	9/49	0·24 (0·07– 0·82)
Hartikainen-Sorri *et al.* (1980)‡	15/39	9/38	1·97 (0·76– 5·15)
Yemini *et al.* (1985)	5/39	14/40	0·30 (0·11– 0·84)
LeVine (1964)§	2/15	3/15	0·63 (0·10– 4·15)
Johnson *et al.* (1975)	2/18	12/25	0·19 (0·05– 0·70)
Typical odds ratio			0·50 (0·30– 0·85)
Birthweight <2500 g			
Hauth *et al.* (1983)	6/80	8/88	0·81 (0·27– 2·42)
Papiernik-Berkhauer (1970)	2/50	8/49	0·26 (0·07– 0·96)
Yemini *et al.* (1985)	5/39	14/40	0·30 (0·11– 0·84)
LeVine (1964)	3/15	2/15	1·59 (0·24–10·51)
Johnson *et al.* (1975)	4/18	11/26	0·42 (0·12– 1·46)
Typical odds ratio			0·46 (0·27– 0·80)
Perinatal death excluding lethal malformation			
Hauth *et al.* (1983)	3/80	3/88	1·10 (0·22– 5·61)
Papiernik-Berkhauer (1970)	0/49	0/47	1·00
Hartikainen-Sorri *et al.* (1980)	4/78	2/76	1·94 (0·38– 9·87)
Yemini *et al.* (1985)	0/39	0/40	1·00
LeVine (1964)	1/15	0/15	7·39 (0·15–99·99)
Johnson *et al.* (1975)	0/18	7/26	0.14 (0·03– 0·71)
Typical odds ratio			0·76 (0·31– 1·90)
Respiratory distress syndrome			
Hartikainen-Sorri *et al.* (1980)	10/78	4/76	2·48 (0·83– 7·42)
Yemini *et al.* (1985)	1/39	4/40	0·29 (0·05– 1·75)
Typical odds ratio			1·39 (0·54– 3·54)
Hyperbilirubinaemia			
Hartikainen-Sorri *et al.* (1980)	8/78	8/76	0·97 (0·35– 2·73)
Yemini *et al.* (1985)	4/39	11/40	0·33 (0·11– 1·01)
Typical odds ratio			0·59 (0·28– 1·26)

* These data refer to women excluded after randomization because they miscarried; the 'miscarriages' analysed by Goldstein *et al.* (1989) all occurred from 20 to 28 weeks and are defined here as preterm births.

† Defined as <38 weeks in this study.

‡ Includes three preterm births after induction of labour which were excluded by Goldstein *et al.* (1989).

§ Excludes one birth of a baby weighing less than 2·5 kg at term, which was included by Goldstein *et al.* (1989).

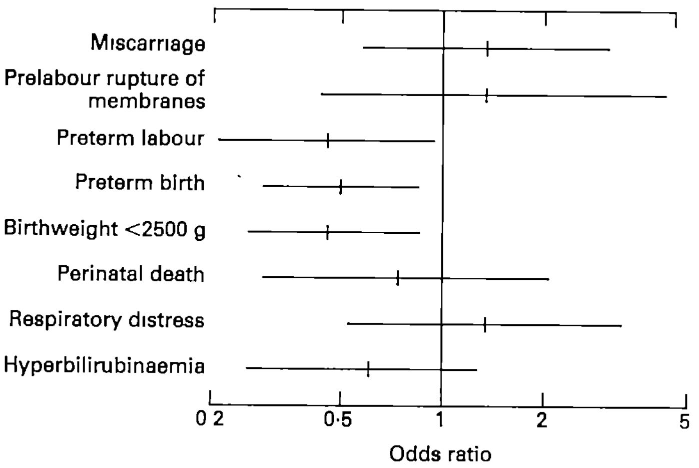

Fig. 1. Effects of 17α-hydroxyprogesterone acetate in pregnancy: typical odds ratios with their 95% confidence intervals, all of which are wide; only those that do not cross the vertical line drawn at unity reach the conventional level of statistical significance ($P<0{\cdot}05$).

can be concluded that there is currently no evidence from controlled trials, or from careful assessment of other clinical data (Macdonald 1989), to justify the clinical use of any progestational agent to prevent miscarriage. The large trial currently being conducted by Daya (unpublished observations) should help to clarify whether or not this approach to the management of recurrent miscarriage has any merit at all.

Although the present analysis lends support to the assessment of Goldstein *et al.* (1989) and of Macdonald (1989) in respect of miscarriage, it is at variance with some of the other findings of Goldstein *et al.* (1989). Thus, the trials of 17α-hydroxyprogesterone caproate showed a statistically significant reduction in the frequency of preterm labour, preterm birth and low birthweight. The effects of 17α-hydroxyprogesterone on the frequency of preterm birth (Table 2) were consistent among trials except for the trial of Hartikainen-Sorri *et al.* (1980), which was the only one not dealing with singleton pregnancies. It is possible that twin pregnancies are different in this respect, and that beneficial effects of 17α-hydroxyprogesterone are confined to singleton pregnancies. However, this is a hypothesis generated, but not tested by the present analysis.

Of the various possible effects of progestogens considered by Goldstein *et al.* (1989), a beneficial effect on 'premature birth' emerged as the most plausible. My analysis included all published placebo-controlled trials of a single, well-defined agent, irrespective of the number of outcome measures on which data were available; it thus included all 17α-hydroxyprogesterone caproate trials studied by Goldstein *et al.* (1989) as well as the trial of Shearman (1968), which they had excluded because it provided data only on miscarriage. It is, however, possible that selective reporting of some outcomes, but not others in particular trials, has yielded biased overall estimates of the effects of this drug (Chalmers *et al.* 1989).

In their recent study and others to which they referred, Goldstein *et al.* (1989) have accorded a great deal of attention to heterogeneity testing among trials. For clinicians this issue is relevant in as much as it helps to guide the choices that need to be made in practice (Chalmers *et al.* 1989). If heterogeneity is important and shown to be present (Goldstein *et al.* 1989), the first clinical question that arises is whether the clinical treatments are actually comparable enough to be included in a single analysis. My analysis is based on the view that the array of progestational treatments, included in the analysis reported by Goldstein *et al.* (1989), was too wide in view of the differences in chemical structures of the agents concerned.

The present study indicates that injections of 17α-hydroxyprogesterone caproate may reduce the occurrence of preterm birth among women so treated. The evidence therefore does not uphold the opinions of Goldstein *et al.* (1989) and Macdonald (1989) that no benefits have been demonstrated of progestogen treatment in pregnancy.

Admittedly, demonstration of a statistically significant effect does not necessarily imply that the effect is also clinically relevant. Similarly, absence of statistical significance does not necessarily indicate that clinically important effects would have been revealed, if they were present. This should be duly considered in view of the small power of the individual trials and the wide confidence intervals even across trials. Nevertheless, a point estimate of a 50% reduction in the odds of preterm birth (with a 95% CI that indicates that this reduction is likely to be comprised between 15 and 70%) cannot be seen as irrelevant. It contrasts too markedly with the poor effectiveness of other efforts to reduce the occurrence of preterm labour and preterm birth (Lumley 1988; Keirse *et al.* 1989). On the other hand, the treatment assessed consisted of repeat injections and was not demonstrated to result in a lowering of perinatal mortality or morbidity, so that further well-controlled research would be necessary before it is recommended for clinical practice.

Currently, the onus is on those who prescribe the treatment to collaborate in obtaining controlled data on substantive outcomes that can settle the question more satisfactorily than it can be at present. Until data from such research are forthcoming, clinicians may be well advised to follow the cautionary approach advocated by Macdonald (1989).

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Social support and pregnancy outcome

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Summary. A total of 509 women with a history of a low-birthweight (LBW, <2500 g) baby were recruited from the antenatal booking clinics of four hospitals and randomized to receive either a social support intervention in pregnancy in addition to standard antenatal care (the intervention group) or standard antenatal care only (the control group). At recruitment to the study, mean gestational age was 6 weeks, mean maternal age was 28·0 years, 86% of the women had one previous LBW baby, 11% had two and 2% had had three or more. The study population was socially disadvantaged: 77% of the women were working class, 18% had unemployed partners and 41% were smoking at booking. Social support was given by four research midwives in the form of 24-h contact telephone numbers and a programme of home visits, during which the midwives provided a listening service for the women to discuss any topic of concern to them, gave practical information and advice when asked, carried out referrals to other health professionals and welfare agencies as appropriate, and collected social and medical information. Pregnancy outcomes were assessed using obstetric case-note data (obtained for 507 women) and a postal questionnaire sent to all mothers 6 weeks after delivery (94% replied). Babies of intervention group mothers had a mean birthweight 38 g higher than that of control group babies; there were fewer very low-birthweight babies in the intervention group. The number of hospital antenatal clinic visits was the same in the two groups (mean 5·1) but more women in the control group (52%) than in the intervention group (41%) were admitted to hospital in pregnancy. Spontaneous onset of labour and spontaneous vaginal delivery were more common in the intervention group, who also used less epidural anaesthesia. The numbers of babies resuscitated at birth and babies admitted to the neonatal unit were similar in the two groups but the babies in the intervention group required less invasive methods for resuscitation and less intensive and special neonatal care. Intervention group mothers and babies were significantly healthier in the early weeks than those in the control group as judged by reported physical and psychosocial health and use of health services. Women's attitudes to the social support intervention were very positive, 80% of those who filled in the postnatal questionnaire singling out that the fact that the midwife 'listened' was important.

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The capacity of social support to promote health has received increasing attention (Cohen & Syme 1985; Dean 1986). An individual's social relationships have been shown to be associated with health status independently of a wide range of medical and other social factors (Berkman 1984). In relation to childbearing, observational studies (Smilkstein *et al.* 1984; Nuckolls *et al.* 1972; Berkowitz & Kasl 1983) of mothers' social networks and relationships suggest that social support improves maternal and infant well-being, including birthweight, and controlled trials of social support in labour (Sosa *et al.* 1980; Klaus *et al.* 1986) provide evidence for the effectiveness of lay support during labour in decreasing perinatal problems and the need for medical interventions in labour and delivery. Furthermore, miscellaneous social interventions in pregnancy (Oakley 1988; Elbourne *et al.* 1989; Elbourne & Oakley 1990) have shown beneficial psychological and behavioural effects of such support. The present study aims to extend our understanding of the potential usefulness of social support in pregnancy by assessing the effectivenesss, in medical and psychosocial terms, of a programme of home visits provided by research midwives to women at above average risk of having a low-birthweight (LBW) baby.

Subjects and methods

Our study population was drawn from the antenatal booking clinics of four hospitals: Derby City Hospital, Pembury Hospital, Tunbridge Wells, the Royal Berkshire Hospital and the North Staffordshire Maternity Hospital in Stoke-on-Trent. The research was approved by the ethics committees in the four hospitals. Women booking for delivery at these four centres were eligible to enter the trial provided they had had at least one previous normally formed baby weighing under 2500 g following spontaneous onset of labour, were less than 24 weeks gestation with a singleton pregnancy, and were fluent in English. A sample size of at least 420 was chosen to give an 80% chance ($\alpha = 0{\cdot}05$) of identifying a difference in the mean birthweight of 150 g, assuming a standard deviation (SD) of 550 g.

One research midwife was employed in each centre to recruit women and to provide the social support intervention. Between January 1986 and May 1987 a total of 534 eligible women were informed about the study, of whom 509 agreed to participate. The midwife telephoned the coordinating centre for the random treatment allocation, which was organized in balanced blocks, stratified by centre: 255 of the women were allocated to the intervention and 254 to the control group.

The social support intervention consisted of a 'minimum package' of three home visits to be carried out at 14, 20 and 28 weeks gestation, plus two telephone contacts or brief home visits in between these times. The midwives were also asked to provide as much support as the mothers asked for, within the constraints of their own case-loads, and were supplied with radiopagers so that they could be 'on call' to the mothers 24 h a day. We designed semi-structured interview schedules to provide a basis for a flexible and open-ended communication between the midwives and the mothers, so that the mothers would feel able to discuss any topic concerning their pregnancy needs and circumstances that was important to them. The research midwives were asked to give advice or information about specific topics only if requested to do so by the mother. They did not give any clinical care, but referred women to the hospital, general practitioner, or community midwives where appropriate: other referrals, for example to social workers, were also carried out as judged necessary by the mother and midwife. Each midwife filled in a form for every contact she had with any woman she was supporting, noting who had initiated the contact, its purpose, content, length and result (e.g. action taken, if any). Parts of the three main home contacts were tape-recorded in order to generate some qualitative data on the nature of the intervention, and on women's experiences of high-risk pregnancy.

Information about the outcome of the pregnancy was obtained from hospital case-notes for 507 of the 509 women (two women who moved were lost to the study). A questionnaire was posted to the mothers from the coordinating centre 6 weeks postnatally: 477 (94%) replied, 243 (96%) in the intervention group and 234 (92%) in the control group. The base for calculating percentages hence varies depending mainly on the source of information for particular variables Chi-squared and Student's *t*-tests were used for discrete and continuous variables respectively. Ninety-five per cent confidence intervals (CI) of the relative risks were calculated where appropriate using the method recommended by Katz *et al.* (1978).

Results

The groups were comparable in important respects at trial entry, in particular with respect to the numbers having more than one previous LBW baby, 35 (14%) in the intervention group and 34 (13%) in the control group, and being currently unsupported (no living-in partner), 41 (16%) in the intervention group and 49 (19%) in the control group (Table 1). According to such criteria, the women in the study were at higher than average risk, not only obstetrically, but socially. Of the 507 women with case-note information, five sets of twins (three in the intervention, two in the control group) were diagnosed after randomization; we have excluded these from the analysis, as this is principally a trial of social support in singleton pregnancy. There were four terminations (two in each group) and 12 miscarriages (six in each group, all below 1000 g).

Of the 243 women remaining in the intervention group, 238 (98%) were seen at home at least once, and 224 (92%) at least three times (Table 2). The average time in pregnancy of the home visits was later than intended, due to later than expected booking at the four centres. At each visit fewer than half the women were referred elsewhere for professional help. Information about specific topics such as smoking was requested by a minority of mothers. One hundred and seventy mothers (70%) received more than the minimum package of contacts with the midwife, 12 (5%) received the minimum package, and 61 (25%) less than this, the usual reason being early delivery. The most important single aspect of the research midwife's help mentioned by the mothers when they were surveyed after delivery was that the midwife listened. Most (94%) of the mothers considered the research midwife very, particularly or quite helpful (Table 2).

Table 3 summarizes the main features of pregnancy, labour and delivery. The main difference between intervention and control women antenatally was that control group women were significantly more likely to be admitted to hospital (relative risk (RR) 0·82; 95% CI 0·64–0·95). Spontaneous onset of labour (RR 1·10; 95% CI 0·98–1·23) and spontaneous vaginal delivery (RR 1·08; 95% CI 0·98–1·18) were more common in the intervention group, which also made less use of epidural anaesthesia (RR 0·69; 95% CI 0·43–1·09).

There were three stillbirths in the intervention group; two were intrapartum and associated with placental abruption (one also with a bicornate uterus) and one was antepartum at 36 weeks due to placental insufficiency (birthweight 1760 g). Of the 483 livebirths, there were five neonatal deaths (two in the intervention and three in the control group).

Birthweight and gestational age at delivery are given in Table 4. Mean birthweight of all

Table 1. Description of groups at trial entry

	Intervention (n = 254–255)		Control (n = 253–254)	
	Mean	SD	Mean	SD
Gestational age (weeks)	15·7	3·5	15·6	3·5
Maternal age (years)	27·9	4·9	28·1	5·3
	No.	%	No	%
Women <20 years of age	9	4	10	4
Previous LBW baby: 1	220	86	220	87
2	28	11	29	11
3+	7	3	5	2
Smoking at booking	104	41	102	40
Married or cohabiting	214	84	205	81
Working class (partner's occupation)*†	194	78	178	75
Partner unemployed*†	44	18	46	19
Employed in pregnancy*†	77	30	79	34
Ethnicity Afro-Caribbean/Asian*‡	11	5	12	5

* Information provided by mother postpartum.
† n = 247–253; 235–238
‡ n = 225, 223.

Table 2. Description of the intervention

	Home contact					
	First		Second		Third	
A. Structure and content						
Number of women seen	238		235		224	
Intended gestational age (weeks)	14		20		28	
Actual gestational age (weeks)						
Mean (SD)	17·8	(3·3)	24·0	(4·6)	29·7	(8·5)
	No.	%	No.	%	No.	%
Referrals to:						
health professionals	44	19	58	25	51	23
welfare agencies	42	18	27	12	19	9
no referral	125	53	129	55	131	59
Information given about:						
smoking	19	8	12	5	2	1
diet	24	10	24	10	19	9
alcohol	12	5	8	3	1	<1
work	12	5	10	4	4	2
other	59	25	36	15	30	13
no 'lifestyle' information	142	60	156	66	178	80
B. Women's views†						
Women felt it important that midwife:						
listened					188	80
gave advice					154	65
saw her throughout pregnancy					131	56
gave information					131	56
was a midwife					79	33
Women considered the midwife:						
very/particularly helpful					115	50
quite helpful					102	44
Total women providing information					236	100

†Information from postnatal questionnaire.

singleton babies was 38 g higher (95% CI −72·6 to 146·6) in the intervention group. Mean gestational age was the same in the two groups.

Summary measures of the postnatal health of babies and mothers are shown in Table 5. Similar numbers of babies in the intervention and control groups were resuscitated at birth (159 and 162) and went to the neonatal unit (35 and 37) but there was a significant difference in method of resuscitation used, with intervention babies requiring less invasive methods. These babies also required less intensive and special neonatal care.

Mothers and babies in the intervention group were significantly healthier than those in the control group as judged by reported health and use of the health services (Table 5). Psychosocial measures, particularly the question 'Are you worried about your baby?' asked in the postnatal questionnaire also showed differences in favour of women who had received social support in pregnancy (Table 5).

Discussion

Our trial of social support in pregnancy was carried out on a population of highly disadvantaged women. For example, three-quarters were working-class, and the incidence of stressful life-events and chronic problems such as inadequate housing was high. These social problems were additional to the problems posed by poor obstetric history. The study was successful in terms of giving the intervention as planned. However,

Table 3. Features of pregnancy, labour and delivery

	Intervention		Control	
	($n = 233$–243)		($n = 225$–243)	
	Mean	[SE]	Mean	[SE]
Hospital antenatal clinic visits	5·1	[0·17]	5·1	[0·17]
	No.	%	No.	%
More than one ultrasound scan in pregnancy	178	76	187	80
Antenatal cardiotocography	97	40	118	49
Antenatal hospital admission	99	41	126	52
Days in hospital Mean [SE]	7·2	[1·1]	8·3	[1·1]
Admission for threatened preterm delivery	34	14	43	18
Raised blood pressure with proteinuria*	8	8	11	11
Pregnancy-induced hypertension	22	9	23	10
Depressed in pregnancy	31	13	40	18
Onset of labour				
spontaneous	180	74	163	68
induced	53	22	64	27
prelabour caesarean	10	4	14	6
Epidural anaesthesia	27	11	39	16
Length of labour Mean [SE]†	5·7	[0·3]	5·9	[0·3]
Type of delivery:				
spontaneous vaginal	197	81	182	75
instrumental vaginal	5	2	11	5
caesarean section	41	17	50	21

* $n = 98$; 104
† $n = 202$; 192.

one consequence of the method of recruitment into the study that was used was a degree of 'overflow' of support to the control group, some of whom said in the postnatal questionnaire that they felt themselves to be part of the study (for example, 16 (7%) said they found the visits of the research midwife helpful, even though she had not in fact visited). This may have resulted in a narrowing of the differences found.

Our results confirm the findings of existing

Table 4. Birthweight and gestational age

	Intervention				Control			
	No.	%	Mean	SE	No.	%	Mean	SE
Birthweight,								
all singletons	243	100	2944	38·5	243	100	2907	40·3
Birthweight distribution (g):								
< 1500	4	2			9	4		
1500–2499	41	17			43	18		
2500–3999	194	80			184	76		
4000+	4	2			7	3		
Gestational age (weeks)			38·6	0·2			38·6	0·2
< 28	4	2			3	1		
28–32	8	3			9	4		
33–36	31	13			34	14		
37 +	200	82			197	81		

Table 5. Postnatal health of baby and mother

	Intervention (n = 230–240)				Control (n = 226–243)			
	No	%	Mean	SE	No.	%	Mean	SE
Baby								
Apgar < 7 at 5 min†	4	2			8	4		
Endotracheal intubation‡	7	5			13	8		
Respiratory distress	7	3			13	5		
To neonatal unit	35	15			37	15		
Ventilated (mean days)	8	3	5·0	1·05	13	5	6·2	1·00
Supplemental O_2 (mean days)	9	4	3·6	1·01	16	7	8·9	2·38
Totally/intravenously tube-fed (mean days)	13	6	6·6	2·15	13	5	18·6	3·18
Breastfed at discharge*	105	46			89	39		
Problems after discharge*	56	24			73	32		
Health service use after discharge*	138	60			156	69		
Mother	(n =230)				(n =226)			
Health not 'good' or 'very good'	69	30			89	39		
Hospital visit (excl. routine postnatal)	10	4			19	8		
Visit to/from GP	62	27			72	32		
Depressed after birth	92	40			107	47		
Feeling of low/no control over life	65	28			83	37		
Worried about baby	36	16			63	28		
Partner helpful								
with other children§	190	88			168	81		
domestically¶	198	97			177	92		

* Information taken from mothers' questionnaires
† n = 206; 215.
‡ n = 157; 155
§ n = 205; 193
¶ n = 217; 208.

studies showing that the provision of 'social' care for pregnant women has the capacity to affect a range of pregnancy outcomes. Previous studies include: trials of mothers holding their own case-notes (Lovell *et al.* 1987; Elbourne *et al.* 1987); continuity of care provided by midwives (Flint & Poulengeris 1987); home visits by midwives (Spira *et al.* 1981) or child health nurses (Gutelius *et al.* 1977; Olds *et al.* 1986); discussing ultrasound scans with mothers (Reading *et al.* 1982); the provision of community-based antenatal care (Reid *et al.* 1983). Two recent overviews of such studies (Oakley 1988; Elbourne & Oakley 1990) show that supported mothers are more likely than the control women to feel 'in control' during pregnancy and postpartum, to be satisfied with their medical care, not to feel unhappy after the birth, to have partners who feel involved with the baby, to be breastfeeding, and to report physical well-being and to have babies with fewer worrying health problems. The effects of social support on the outcomes of mean birthweight, LBW and preterm delivery are less clear cut.

The mean birthweight difference we found in our study is of the same order as is found in controlled trials of dietary intervention in pregnancy (Rush *et al.* 1980), which suggests that our initial aim of increasing birthweight by 150 g was over-ambitious. (This aim was chosen both because it is in the region of the birthweight difference associated with maternal smoking, and because to have aimed for a lower figure would have meant increasing the sample size and therefore the costs of the study.) It is hoped that the results of a number of social support trials (Heins & Nance 1986; Heins *et al.* 1990; Stanley & Bryce 1986; Scott 1984; Hobel and Bemis 1986; Spencer & Morris 1986; Spencer *et al.* 1989) will clarify this particular question in the future. In our study we did not aim to influence the LBW rate as such, and the difference between our groups is small, though there is some suggestion of an effect on the very low-birthweight baby. On the other hand, our study does show that the benefits of social support can be manifested in the area of medical care (in pregnancy, labour, delivery and postnatally). The improved emotional well-being of the socially supported mothers in our study is consistent with the findings of other studies. Fewer physical health problems among intervention group mothers and babies after discharge from hospital may reflect the greater confidence and happiness of mothers, or real physical health effects of the social support intervention, or both. A sign test based on the 15 hypotheses of the study prespecified in the original protocol shows that the probability of our data favouring the intervention group for 13 of these (as it does) is 0·0009. However, this needs to be interpreted conservatively as the hypotheses were not all independent.

Whatever the results of other social support in pregnancy trials, it is unlikely that social support will ever be shown to override the cumulative effects and problems of social disadvantage, many of which our research midwives encountered in giving support in this study (Buckle 1988). For example, it is known that the high rate of smoking among working-class women (observed in our study) is in part a response to the stress of caring for families in difficult circumstances (Graham 1987). In our study, and others, smoking can be linked to various indices of material conditions. For example, we found an inverse relation between income and smoking, with 56% of women living at or below supplementary benefit level smoking, as against 27% of those whose income was 300% or more of that level. Smoking in pregnancy is also associated with a depression in mean birthweight (in our study the mean birthweight of babies of smokers was 2837 g compared with 2994 g for babies of non-smokers). These considerations constrain the impact a social support intervention is likely to have. Although the policy implications of our findings must be in the direction of promoting continuity of care and a less impersonal and more sensitive antenatal service, it is important to remember that social policy changes are also needed to improve the health-denying conditions in which many mothers and babies live.

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Change in ovarian arterial compliance during the human menstrual cycle assessed by Doppler ultrasound

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Summary. Ovarian arterial velocimetry, using real-time two-dimensional and pulsed Doppler ultrasound, was performed on 36 occasions in nine healthy women with regular menstrual cycles. The change in ovarian arterial compliance was based on the calculation of pulsatility index (PI). In the active ovary carrying a dominant follicle or corpus luteum, the PI in the early follicular phase (mean 6·97, SD 2·01) was significantly higher than that in the late follicular phase (mean 2·36, SD 0·31) ($P<0\cdot001$), and the PI in the early luteal phase (mean 0·68, SD 0·09) was significantly lower than that in the late follicular phase ($P<0\cdot001$). The PI in the late luteal phase (mean 0·93, SD 0·16) was significantly higher than that in the early luteal phase ($P<0\cdot01$). In the inactive ovary, no cyclical changes were seen in the values of PI. There was a significant difference between the values of PI in the active ovary and the inactive ovary in the late follicular, the early and the late luteal phases [2·36 (SD 0·31)] *vs* [6·29 (SD 1·02)], [0·68 (SD 0·09)] *vs* [6·18 (SD 1·33)], [0·93 (SD 0·16) *vs* [6·57 (SD 1·72)] ($P<0\cdot001$), respectively. Use of non-invasive Doppler ultrasound to study physiology of ovarian haemodynamics during the menstrual cycle is of great clinical relevance and paves the way for further investigations on sterility.

Doppler ultrasound has been widely used to detect various blood flow conditions of deeply located pelvic vessels in women (Hata *et al.* 1988*a*; Taylor & Burns 1985; Taylor *et al.* 1985*b*). Myometrial arcuate arterial velocimetry by Doppler ultrasound revealed changes of myometrial arcuate arterial haemodynamics throughout the reproductive cycle (Hata *et al.* 1988*a*). We also reported that Doppler ultrasound might be a pertinent diagnostic tool for detecting intrapelvic neoplastic tissues and other abnormal changes (Hata *et al.* 1988*b*).

Although the feasibility of studying ovarian arterial blood flow has been demonstrated (Taylor *et al.* 1985*a*), the change in ovarian arterial compliance during the menstrual cycle is not well understood. We report here our findings on normal ovarian haemodynamics, using real-time two-dimensional and pulsed Doppler ultrasound.

Subjects and methods

Nine healthy Japanese women with regular menstrual cycles were recruited to the study. Their

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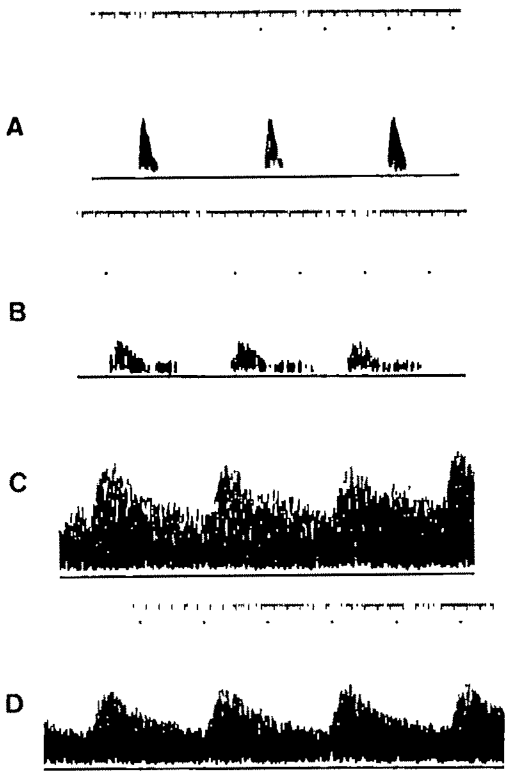

Fig. 1. Arterial blood flow velocity waveforms in the active ovary during the menstrual cycle. (A) early follicular phase; (B) late follicular phase; (C) early luteal phase; (D) late luteal phase.

mean age was 27·0 years (range 21–31). Each woman was investigated with real-time two-dimensional and pulsed Doppler ultrasound on four occasions during the menstrual cycle on days 5–7 (early follicular phase), 11–13 (late follicular phase), 15–17 (early luteal phase) and 26–28 (late luteal phase).

A total of 36 examinations was performed; only one observation was made in each woman in each of the four phases of the cycle. Permission for the study was obtained from each woman.

The apparatus used was an Aloka SSD-870 with a 3·5 MHz transducer, in either the two-dimensional and/or pulsed Doppler mode. The flow directed to the transducer is displayed in red, the flow directed away from the transducer is in blue. Pulse repetition frequencies of this apparatus were 4~26 kHz. Blood flow velocities were displayed within a 28° to 90° sector, at a depth ranging from 4 to 22 cm. This apparatus allows for simultaneous real-time imaging and pulsed Doppler tracing. In the two-dimensional and pulsed Doppler modes, velocities can be measured for up to 6·2 m/s. Wall filters (100 Hz) were used to eliminate low-frequency signals occurring from all noise.

Using the full-bladder technique, real-time two-dimensional Doppler ultrasound was used and the ovaries were recorded as active or inactive depending on the presence of a dominant follicle or corpus luteum. Ovulation was confirmed by the disappearance of a dominant follicle and by changes in basal body temperature. On a real-time two-dimensional echogram, the sampling point on the line of the pulsed Doppler beam was placed at the region of interest, where the coloured ovarian arterial flows were noted, otherwise pulsation of the ovarian artery was identified in the substance of ovary. When the ovarian artery was not seen on the real-time image, the sampling point was moved within the substance of ovary until arterial signals could be obtained. Blood flow velocity waveforms were displayed in real time on a monitor oscilloscope and recorded on glossy black on white electrostatic paper at a speed of 50 mm/s. The formula

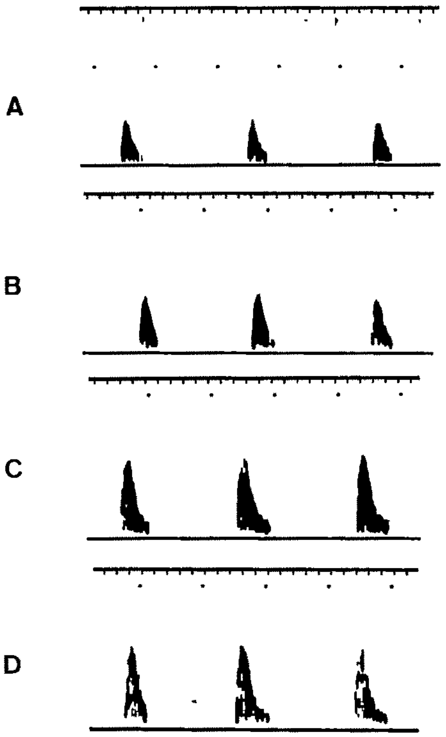

Fig. 2. Arterial blood flow velocity waveforms in the inactive ovary during the menstrual cycle. (A) early follicular phase; (B) late follicular phase; (C) early luteal phase; (D) late luteal phase.

Table 1. Ovarian arterial pulsatility index (PI) in the active and inactive ovaries during the menstrual cycle measured in nine women

Phase of cycle	Active ovary	Inactive ovary
Early follicular	6·97 (2·01)[a]	6·82 (1·47)
Late follicular	2·36 (0·31)[b]	6·29 (1·02)[bb]
Early luteal	0·68 (0·09)[c]	6·18 (1·33)[cc]
Late luteal	0·93 (0·16)[d]	6·57 (1·72)[dd]

Results are means (SD).

Significance of differences a *vs* b, b *vs* c, b *vs* bb, c *vs* cc, d *vs* dd: $P<0·001$; c *vs* d: $P<0·01$.

used was pulsatility index (PI) (Gosling & King 1975), defined as the difference between maximum systolic frequency and maximum end-diastolic frequency divided by time averaged maximum frequency, calculated as average value obtained from five consecutive waves.

Statistical analysis was performed by paired t-test after log transformation.

Results

The blood flow velocity waveforms obtained from both ovarian arteries during the menstrual cycle are shown in Figs 1 and 2. Table 1 summarizes the mean PI (SD) at each phase in both active and inactive ovaries during the menstrual cycle. In the active ovary, the PI value showed dramatic changes during the menstrual cycle, but the PI was almost constant throughout the menstrual cycle in the inactive ovary. A significant difference was seen in the values of PI between the active and inactive ovaries, at the late follicular, the early and the late luteal phases, respectively.

Discussion

Various indices have been used to quantify the pulsatility in assessing arterial blood flow velocity waveforms (Gosling & King 1975; Pourcelot 1974; Stuart *et al.* 1980). The PI is probably the most accurate reflection of pulsatility and peripheral resistance changes, particularly when end-diastolic Doppler shifts fall below filter frequency (Griffin *et al.* 1983). We noted a remarkable change of ovarian arterial compliance during the menstrual cycle. In the active ovary diastolic Doppler shifts increased slightly in the late follicular phase and a relatively high diastolic flow and low pulsatility, consistent with vasodilatation, was seen at the early and late luteal phase (Fig. 1). In the inactive ovary the waveform revealed no diastolic flow, and it seemed to be a high distal vascular impedance throughout the menstrual cycle (Fig. 2). Numerically, the most dramatic change occurred between the early and late follicular phases (Table 1) End-diastolic flow is generally acceptable as an index of peripheral resistance in assessing the pulsatility of the peripheral vessel (Griffin *et al.* 1983). In the late follicular phase, there was a low diastolic component in the active ovary but end-diastolic flow was absent. However, in the early luteal phase, diastolic flow in the active ovary was evident and end-diastolic flow increased remarkably (Fig. 2) This suggests decreased vascular impedance, implying increased blood flow, between the late follicular and early luteal phases.

Folliculogenesis, ovulation and start of menstruation are regulated by various hormones secreted from the pituitary, hypothalamus and ovary (Novak & Woodruff 1976). Progesterone is one of those hormones, and is mainly produced by granulosa cells of the ovary (Pritchard *et al.* 1985). The first measurable quantity of progesterone is on the 14th day of the menstrual cycle and the levels increase to a maximum by the 16th day and remain elevated until the 24th day of the cycle, after which there is a gradual decline until the onset of menstruation (Hoffman 1948). The main effects of progesterone are conversion of a proliferative to a secretory endometrium and inhibition of the contractility of smooth muscle (Pritchard *et al.* 1985) From a study in rhesus monkeys, diZerega *et al.* (1980) reported that despite perfusion of both ovaries with the same peripheral blood, once a dominant follicle was identified, levels of oestrogens, androgens and progesterone were dramatically elevated in the venous effluent from the ovary containing that follicle. Disparate secretion of progesterone became evident at 2 or 3 days before the mid-cycle (diZerega & Hodgen 1981). The PI changes in the active ovarian artery and the high PI values of the inactive ovarian artery during the menstrual cycle may reflect these physiological and endocrinological changes. Brown *et al.* (1980) reported Doppler ultrasound findings obtained from conscious ewes that appear to confirm our results. The velocity of the arterial blood supply to the ovary with a corpus luteum, but not of that to the contralateral ovary without a corpus luteum, was minimal from day 1 to day 2 inclusive (day 0 = day of oestrus), increased steadily until day 13 (−4) and then declined precipitously. Arterial blood velocity to the ovary with a corpus luteum and progesterone levels in peripheral plasma were highly correlated (Brown *et al.* 1980).

We obtained evidence for the transition of ovarian arterial complicance during the menstrual cycle, based on the calculation of PI by Doppler ultrasound. This approach to elucidating the physiology of ovarian haemodynamics provides a foundation for studies on the pathophysiology of various disorders throughout the menstrual cycle, particularly those related to ovarian function.

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Endemic placenta accreta in a population of remote villagers in Papua New Guinea

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Summary. Using a combination of prospective registration of definite cases ($n = 47$) and retrospective identification of probable cases ($n = 22$) over a 6·5-year period, we have estimated that the rate of placenta accreta in the Milne Bay Province of Papua New Guinea is at least 1·6 per 1000 births, and probably in excess of 2·3 per 1000. This is substantially higher than other reported estimates of the frequency of this condition, which causes significant maternal morbidity. The study population of 130 000 consisted mainly of subsistence cultivators who live in remote hamlets, and included about 27 600 women between the ages of 15 and 49 years. A number of factors seem likely to be important in the aetiology of the condition in Milne Bay Province, including infection associated with previous childbirth and abortion. Over three-quarters of the cases would have been prevented if all women of para ≥4 or with a history of retained placenta had used effective contraception. Better obstetric care, including early treatment of postpartum sepsis and incomplete abortion, may also help to reduce the frequency of placenta accreta in this population.

Placenta accreta is characterized by abnormal adherence of the placenta to the myometrium. It can be partial with one or more lobules affected, or total. The condition is now relatively rare in developed countries, with a rate of about 0·1 per 1000 births (Breen *et al.* 1977; Fox 1972, 1978; Luke *et al.* 1966; Millar 1959). Large differences in reported rates, from 0·01 per 1000 at the Johns Hopkins Hospital in the USA (Eastman 1954) to 1·9 per 1000 at the Chiengmai Hospital in Thailand (Sumawong *et al.* 1966), remain unexplained. Many of the reported rates, however, are substantially affected by differences in case definition; in addition, most rates have been based upon retrospective hospital reviews, without population-based denominators.

In Papua New Guinea, retained placenta, including placenta accreta, has been recognized to be an important cause of maternal morbidity and mortality for at least the past 50 years (Braun 1967). At present the histopathology services and some obstetric practitioners have noted large and unexplained differences in the rates of placenta accreta among different provinces. The Port Moresby Hospital in the national capital was the only source of histopathology services in the country during a period of 3 years, 1980 to 1983, when 30 specimens of placenta accreta were seen there; 25 came from Milne Bay Province and the remaining five from rural

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areas of the other 19 provinces. There were no cases from the urban capital district of 130 000 people surrounding the Port Moresby Hospital. The present prospective case study from Milne Bay Province, carried out over 6·5 years, provides an estimate of the incidence of placenta accreta in a population of 130 000 Melanesian subsistence cultivators, who live mainly in remote hamlets on scattered tropical islands and mountains in an isolated rural province.

Subjects and methods

Study population

The Provincial Hospital at Alotau has 100 beds and is the only hospital with surgical facilities for the population of Milne Bay Province. Most people live in tiny hamlets of a few huts, many along the coast, but some inland in mountainous areas. Complicated obstetric cases, including most patients with retained placenta for periods of >24 h, are referred to the Provincial Hospital from 32 outlying rural health centres by nursing staff or health extension officers. Transport is difficult due to isolation and absence of roads, and includes footpaths, canoes, boats, and light aircraft. Fortunately, health centres are equipped with radios and most are located near small airstrips, which facilitates emergency evacuation of patients (Barss & Blackford 1983). Since the government provides free air transfer of medical emergencies to hospital, most patients who reach a health centre can be transferred to hospital when this is necessary. Most of the patients included in this study are drawn from this group. However, since most deliveries still occur in the villages, an unknown number, probably considerable, of patients with retained placenta die at home without ever reaching a health centre.

There were 2736 deliveries at the provincial hospital during the study period. The crude birth rate was calculated at that time by census officials to be 35 per 1000; it was therefore estimated that there were about 29 600 births in the provincial population of 130 000 during the study period. At the time of the 1980 National Census, there were 27 607 women in the age group 15–49 years.

Definite cases of placenta accreta

Prospective registration of definite cases of placenta accreta began in November 1978 (when it was first noted that placenta accreta appeared to be unusually common in the population), and continued until April 1985, a period during which one of us (P.B.) was stationed continuously at Alotau Hospital. All patients undergoing hysterectomy for presumed placenta accreta were considered for inclusion as 'definite' cases, as well as one patient who had died at a health centre but where a post-mortem specimen of the uterus had been obtained. The uteri were opened postoperatively (and the gross appearance recorded), fixed in formalin, and sent for histopathology. A histopathologist (K.A.M.) reviewed all 40 cases for which histopathology slides were available, as well as many of the fixed specimens. 'Definite' cases of placenta accreta included those that were confirmed by the typical histological features of complete or partial absence of decidua basalis and direct attachment of placental villi to the muscularis (Fig. 1), as well as a few cases where specimens had the typical gross findings of dense adherence of placental tissues to extensive areas of the myometrium (Fig. 2) but where histopathology was unavailable due to loss in transit or inadequate fixation. Cases were not subdivided into placenta accreta, increta, or percreta on the basis of depth of penetration, since features of all three were sometimes evident in the same specimen. It is likely that the underlying pathological process is similar in most cases, with severity dependent upon the degree of prior damage to the cavity of the uterus.

Questionnaires, which included details of the present pregnancy as well as known or suspected risk factors for placenta accreta, were used for patient interviews, which were done by one author (P.B.) with the help of local nurses for translation. Detailed operating room records were also maintained. All patients who underwent hysterectomy were operated upon by the same person (P.B.), who also carried out or supervised most of the manual removals of retained placentas. One of the reported cases was transferred elsewhere. Details for a few patients discharged without adequate histories were obtained from questionnaires sent to their health centre nurses. Since most of the patients had already been delivered, the parity recorded included the current pregnancy.

Probable cases of placenta accreta

It has been asserted that many cases of placenta

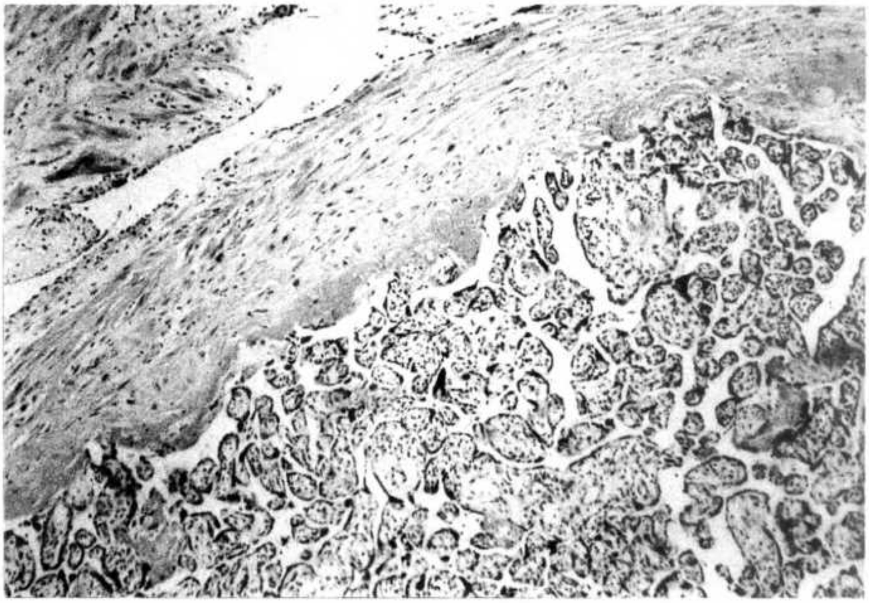

Fig. 1. Placenta accreta with villi attached directly to myometrium. Patient was gravida 6, para 6, who had had a 'rot-out' of a retained placenta in the preceding pregnancy. × 140.

accreta go unreported (Millar 1959). This problem arises because the generally accepted case definition is based upon histological confirmation; in cases where the uterus is not removed and is unavailable for histological study, a definite diagnosis cannot be assigned. Therefore, in addition to prospective registration of definite cases, hospital records of all cases of prolonged retention of the placenta (for periods >24 h) and of a few retained placentas which had been removed by curettage, were reviewed retrospectively to identify 'probable' cases of partial or complete placenta accreta among patients who had not undergone hysterectomy. All late cases of retained placenta (≥24 h) were managed in the operating theatre, and careful records were kept there. From this group, 'probable' cases of placenta accreta were defined to include patients

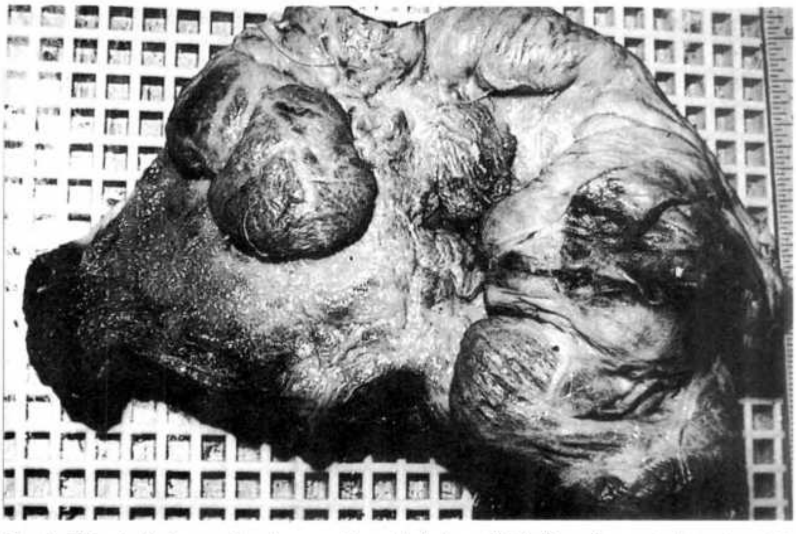

Fig. 2. Bisected uterus showing scattered lobules of totally adherent placenta with intervening bare myometrium covered only with placental membranes.

treated by either manual removal of the placenta or curettage, where the physician had noted that the placenta was abnormally adherent. Also included were several cases treated by the 'rot-out' method and a case diagnosed elsewhere at post-mortem. The term 'rot-out' is used in this paper to describe a technique promoted by one obstetrician for management of prolonged retention of the placenta in Papua New Guinea. The placenta was allowed to gradually slough out or disintegrate inside the uterus, while antibiotics were administered concurrently in the hope of preventing septicaemia. The strong odour which emanated from such patients often necessitated isolation, and in two of six patients treatment ended abruptly when the patient absconded. It is not known whether these patients survived at home; one patient died in hospital. The rot-out method was abandoned in the study, for both aesthetic and medical reasons.

Results

Forty-seven patients were considered to be 'definite' cases of placenta accreta. In all, the gross pathology showed a placenta which was densely adherent to extensive areas of the myometrium; adherence was total in 21 (Fig. 2) and partial in 26. Forty cases were confirmed by typical histological features (Fig. 1); seven specimens were lost in transit, or due to inadequate preservation.

The average parity of the 47 patients was 5 (range 2–12) at the time of presentation; 62% (29/47) were para ≥5. Previous retained placenta, manual removal, rot-out, and postpartum infection were common among their histories (Table 1). Among the patients of para ≥5, 83% (24/29) had a history of one or more of the other listed risk factors. A history of a previous retained placenta was obtained from 66% (19/29) of patients of para ≥5 and from 39% (7/18) of women of lower parity; thus 77% (36/47) of all patients were para ≥5 or had had a previous retained placenta. Of the 47 patients 6 (13%) had no history of any of the listed risk factors.

Forty-six of the 47 patients reached hospital alive, 1–12 days after delivery. Units of blood transfused averaged 4 per patient (range 0–12). One patient died at a health centre from severe haemorrhage as a result of an inverted uterus, after cord traction on a nearly totally adherent placenta. Of the 46 patients who reached hospital alive and who underwent hysterectomy, only one died. This woman died suddenly 4 days after hysterectomy, apparently from pulmonary embolism, believed to be secondary to ovarian vein thrombosis; her preceding pregnancy had also been complicated by a retained placenta, which had been treated at a health centre by the 'rot-out' method. Thus, at least 4% of the women with placenta accreta died.

A further 22 patients during this 6·5-year study are thought likely, on clinical grounds, to have had at least focal areas of placenta accreta. These 'probable' cases were identified retrospectively from the case histories of 59 patients who had been treated for retained placenta during the study period by manual removal, curettage, or the rot-out method. Most placentas had been retained for >24 h, some for as long as 12 days. In 14 women, the placenta had been felt to be abnormally adherent, at the time of manual removal in 11 or curettage in three. In six others the retained placenta had been left to rot out in hospital. One patient had been transferred to a major hospital for presumed placenta accreta; no operation was done, but when death occurred a few weeks later, autopsy was said to have shown placenta accreta and peritonitis. An experienced physician visiting one of our health centres diagnosed another case after an unsuccessful attempt at manual removal; the patient died before transfer.

Although details of past history were not available for all of these 22 patients, it is known that at least 5 of the 11 treated by manual removal had a history of a previous retained placenta, one had had four previous retained placentas and another had had five. One had had a previous caesarean section. Among the six patients treated in hospital by the rot-out method, at least one had had two previous retained placentas, and, in at least four, manual removal of the placenta had been attempted unsuccessfully at a health centre before transfer.

In summary, assuming that the total number of births in the province during the study period was about 29 600, the rate of placenta accreta was definitely at least 1·6 per 1000 births, probably at least 2·3 per 1000 births, and quite possibly higher than this.

Surgical and pathological findings

Occasionally under anaesthetic, an asymmetrical uterine fundus or fundal mass could be pal-

Table 1. Risk factors in 47 patients with definite placenta accreta, Milne Bay Province, Papua New Guinea

Risk factors	No.	%	Remarks
Parity ≥5	29	62	At least 19 (66%) had had one or more retained placentas
Previous retained placenta	26	55	Three had had two or more previous retained placentas, 19 were ≥ para 5
Previous manual removal	16	34	Two of the removals had been done by lay villagers
Previous postpartum infection*	10	21	Five were associated with a previous retained placenta
Previous 'rot-out' of placenta	4	9	Some had been unwell and septic for weeks during the 'rot-out'
Previous miscarriage*	4	9	None had had a previous retained placenta
Previous caesarean section	4	9	Three had no other predisposing factors; in one the accreta was not in the area of the previous uterine incisions
Placenta praevia in present pregnancy	3	6	
None of the above factors	6	13	

* These numbers are believed to be underestimates because of the difficulty in obtaining good histories for these conditions.

pated through a thin abdominal wall. At operation, placental tissue and overlying blood vessels could sometimes be seen through a very thin myometrium, or beneath the serosa. One woman who had been in labour for 7 days at home, arrived still undelivered with a spontaneous perforation in an extensive placenta percreta; it appeared that there was insufficient myometrium to expel the macerated fetus. The myometrium was often thin focally or beneath the entire placental bed. In many cases, deficient lobulation of the placenta was noted; placental membranes were directly adherent to bare myometrium in such areas. The histological findings in all cases were similar, typical of placenta accreta, with complete or partial absence of decidua basalis and placental villi directly attached to the muscularis (Fig. 1), sometimes growing into the blood sinuses for a considerable distance (placenta increta), and in two patients even perforating through the whole thickness of the uterine wall (placenta percreta). In many cases, the inner surface of the myometrium away from the placental site was completely bare of endometrium; sometimes only vestiges of endometrium were seen. No inflammatory reaction in the uterus was noted, unless extreme delay or previous manual interference had allowed infection to occur.

Discussion

It is clear that placenta accreta is remarkably common in some village populations of Papua New Guinea. In a population of 29 500 births, 69 definite or probable case yields an estimated rate of 2·3 per 1000 births. The true rate is almost certainly considerably higher, since only about 10% of deliveries take place in hospital and the overall maternal mortality is believed to be about 1% (Babona *et al.* 1974; Mola & Aitken 1984). The observed rate is much higher than in most other reported studies; for example, among 80 000 births at the Johns Hopkins Hospital in Baltimore, USA, only one case of placenta accreta was identified (0·01 per 1000) (Eastman 1954), and at the Sloan Hospital for Women in New York City, only four cases were found among 70 000 deliveries (0·06 per 1000) (Rotton & Friedman 1957). The high rate in Milne Bay Province is unlikely to be related to over-diagnosis on our part: one of us (P.B.) managed busy obstetric wards in rural hospitals in Angola, Africa, for 2·5 years, and during that time encountered only one case of placenta accreta; the other (K.A.M.) described the first case of diffuse placenta accreta to be reported among 20 000 deliveries during a 14-year period at the North Hertfordshire Hospital, UK (James & Misch 1955).

The only other study reporting a rate of placenta accreta as high as that in Milne Bay Province came from Chiengmai in Thailand (Sumawong *et al.* 1966). The Chiengmai Hospital is located in a city in the centre of a mountainous area populated by hill tribes. Ten cases of placenta accreta were seen among 5400 hospital deliveries, a rate of about 1·9 per 1000 hospital births; however, as the proportion of cases referred from the rural areas is not given, nor the total number of deliveries in the catchment area, the true (population) rate of placenta accreta remains uncertain. Other investigators have also reported high rates of placenta accreta, but unfortunately no gross or microscopic confirmation of the diagnosis was available for most of the patients included in such studies. For example, a rate of 1·3 cases per 1000 hospital births was reported from Chile in a paper published 40 years ago; however, only 19% of the patients underwent hysterectomy (Thonet 1949). Since the rates reported from less developed countries are up to 200 times greater than from some studies in industrialized countries, it appears likely that there are real differences in rates between these two settings, which need to be explained.

Previous damage to the endometrium is believed to predispose to placenta accreta. The trophoblast may invade directly into a bare myometrium rather than into the endometrium, owing to partial or complete failure of the decidua basalis to develop. As seen in Table 1, most of the Milne Bay patients had predisposing factors for this, including previous retained placentas, some of which were treated by manual removal and others by the rot-out method, as well as postpartum infections and miscarriages.

The prolonged sepsis often associated with rotting-out must result in near total destruction of the endometrium, including the basal regenerative layer, and possibly loss of myometrium in severe cases. It is amazing that any of these women managed to achieve another pregnancy, and not surprising that many subsequently presented with placenta accreta totalis. The rot-out treatment has been suggested for use where skilled surgical intervention and transfer are not available (Braun 1967), and it may at times be the best option; however, placenta accreta would be expected to be a serious hazard in future pregnancies.

The observed association between placenta accreta and high parity may reflect the cumulative risk of endometrial damage with repeated pregnancies in Milne Bay Province; 83% of the definite cases who were para ≥5 had a history of one or more other risk factors in addition to high parity. The frequency of puerperal sepsis after village deliveries in Milne Bay Province is unknown but it is assumed to be fairly common. Most village births are assisted by family members, without the use of sterile techniques or antiseptics. The delivery is usually conducted on pandanus mats in a village hut (Poschl 1985*a*, 1985*b*; Poschl & Poschl 1985). Old and often unclean mats are generally used for economy, since they are subsequently discarded. After the birth, the new mother is often confined to the small hut where she gave birth, for about 1 month. The lochia are allowed to drain freely on to the mats upon which the woman sits, which again are often old and soiled, since they are burned at the end of the confinement. A fire is kept burning inside or under the hut to provide warmth for the mother and baby. It is possible that the use of such old and soiled mats in close proximity to the bare perineum, the lack of antisepsis, and perhaps the smoky environment, contribute to the rate of puerperal sepsis or suppurative endometritis. Infections would often not be treated with antibiotics, because of the remoteness of many hamlets, and because of the mandatory seclusion during the puerperium. Septic destruction of the endometrium would likely occur, and has been observed by one of the authors (K.A.M.) in uteri removed for severe puerperal sepsis (Fig. 3).

Previous complicated pregnancies, with prolonged delays in reaching health facilities, could also have resulted in uncontrolled infection. Manual removal of the placenta, often done under less than optimal sterile conditions in villages or health facilities, would also often result in endometrial sepsis and necrosis. Incomplete abortions and missed abortions seldom receive medical attention. Extensive necrosis resulting from undiagnosed and untreated puerperal sepsis could have been the cause of the placenta accreta in some of our patients with no other identifiable risk factors; the extreme pathology noted in some cases of placenta percreta could have resulted from such necrosis, possibly in conjunction with other factors such as the uterine thinning and fibrosis found in many grand multiparae. These and other possible aetiological factors for placenta accreta need to be considered in future studies.

On the basis of the data presented here, however, scope for preventing most cases of placenta accreta already appears to exist. If all women of para ≥4, and all with a history of a previous retained placenta, had used effective family planning, 77% (36/47) of the definite cases of placenta accreta would have been prevented. Patients who have already had a placenta accreta

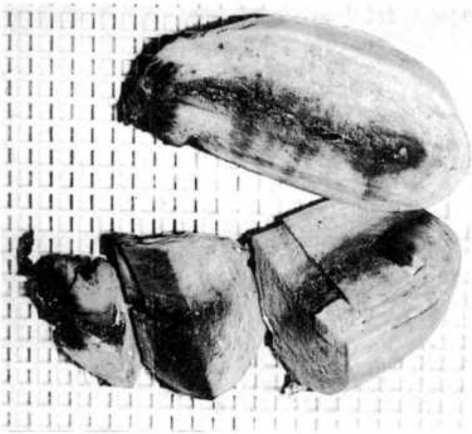

Fig. 3. Uterus removed for severe puerperal sepsis, showing extensive necrosis of endometrium, which may predispose to future placenta accreta.

or rot-out appear to be at particularly high risk of serious complications in future pregnancies, and should be advised accordingly. Although the maternal mortality was low in the hospitalized patients in this series, this would not always be the case. Early and effective treatment of incomplete abortion and postpartum sepsis should also help in prevention. More effective rural obstetric services need to be developed, including better communication and transport links with remote villages and islands. As patterns of high maternal mortality and morbidity and common risk factors for placenta accreta became apparent during this study, we began health education of rural nursing staff and the public by means of refresher courses and local radio broadcasts. An active programme of hospital delivery and tubal ligation was initiated for women of high parity with a history of retained placenta or other risk factors (Barss & McCallum 1983; Barss & Blackford 1985). Subsequently, early referral of cases and high-risk patients improved, and more than 1300 women (85% were para ≥5) underwent tubal ligation. During the last 2 years of the study, there was a significant decrease in the overall number of obstetric emergencies, including placenta accreta (Barss & Blackford 1985). This is not to suggest that we advocate hospital delivery for all women in situations where resources are scarce; nosocomial infections and overall quality of obstetric care are difficult to control in crowded and understaffed wards.

Finally, it is worth noting that placenta accreta appears to be assuming increasing importance as a reason for emergency hysterectomy in the USA. In 1984, it was reported to be the second most common reason for emergency hysterectomy for obstetric haemorrhage (30% of cases) after uterine atony (45%) at the Los Angeles County Women's Hospital (Clark *et al.* 1984). It has been suggested that this may be due to the sharp rise in the caesarean section rate, since that operation is a risk factor for the subsequent development of placenta accreta (Clark *et al.* 1985).

It is also of interest that placenta accreta (as well as uterine sacculation, paper-thin uterine fundus, and uterine dehiscence) has been reported as a complication of pregnancy in patients treated aggressively for Asherman syndrome (Friedman *et al.* 1986), in which endometrial failure occurs when most of the functioning endometrium has been obliterated by scar tissue. This syndrome, in developed countries, almost always follows a single curettage for postpartum bleeding or for an infected abortion, or several curettages at close intervals for abnormal uterine bleeding (Riddick 1986). Missed abortion and genital tuberculosis are other causes (Schenker & Margalioth 1982). The myometrial pathology of thinning and fibrosis sounds similar to that in many of our patients, and the underlying pathological processes could be related; placenta accreta complicated 8% of pregnancies (105/1283) in patients treated for intrauterine adhesions (Schenker & Margalioth 1982).

Case–control studies may be useful to test the various aetiological hypotheses that exist about the origins of this important complication of pregnancy. It is possible that the high rate of placenta accreta described in Milne Bay Province, as compared with other rural areas of Papua New Guinea, resulted from more complete ascertainment due to an unusually well-developed programme of emergency referrals and surgical management within the provincial system; if so, this would indicate a significant unmet need elsewhere in the country. Although a more complete explanation of the observed high rate of placenta accreta may require controlled studies, it is likely that a combination of family planning, health education, and improved obstetric care can provide effective primary prevention of placenta accreta for the women of Milne Bay Province.

Acknowledgments

We acknowledge with thanks the contributions of many people. Many rural health workers resuscitated and referred patients with placenta accreta. Operating theatre staff responded willingly to patients' needs during nights and weekends. No woman died of insufficient blood for transfusion, thanks to the careful work of our small group of blood bank and laboratory staff. Dr Joycelyn Farnsworth, Private Histopathology Laboratory, Royal Canberra Hospital, processed and reviewed several specimens. Dr Iain Chalmers and Dr Ronald Gray provided helpful advice during manuscript revision. Mary Phillips and Becky Ostrowski helped with manuscript preparation. Dr Barss was supported by a Medical Research Council of Canada fellowship during revision of this paper.

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Is routine colposcopic assessment necessary following laser ablation of cervical intraepithelial neoplasia?

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Summary. The colposcopic and cytological findings at follow-up of 1000 women treated by laser ablation for cervical intraepithelial neoplasia or human papillomavirus infection at the Regional Department of Gynaecological Oncology,. Gateshead, were reviewed. Colposcopy detected six of 27 patients with residual disease compared with cytology which was abnormal in 26 of the 27 and detected 21 as abnormal on the first visit after laser treatment. In our unit invasive disease after laser treatment was never detected solely on initial colposcopic review.

Laser vaporization of the cervix using the carbon dioxide laser is a well-recognized treatment for cervical intraepithelial neoplasia (CIN). As long as the transformation zone is ablated to an adequate depth of 8–10 mm, cure rates in excesss of 90% have been reported following a single treatment (Wright *et al.* 1983; Jordan *et al.* 1985).

Long-term follow-up is essential to detect residual and recurrent disease as well as the development of invasive carcinoma (Pearson *et al.* 1989), and has traditionally taken the form of initial colposcopic and cytological review followed by regular cytology.

The purpose of this study was to assess the need for colposcopic assessment following laser ablation.

Patients and methods

In the Regional Department of Gynaecological Oncology, Gateshead, patients with histologically confirmed CIN or human papillomavirus (HPV) infection and satisfactory colposcopy, where the limits of the abnormality can be defined, are treated with the CO_2 laser (Evans & Monaghan 1983). The whole of the transformation zone is treated to a depth of 8–10 mm.

Patients are reviewed 6 months after treatment with colposcopic examination and cervical cytology. If both are normal the patient is discharged back to her general practitioner for annual smears, copies of the results being forwarded to the unit. Any significant cytological abnormality would result in the patient being reviewed colposcopically. All the patients' records are computerized and regularly updated by medical staff.

For the purpose of this study the case records of 1000 patients treated with laser ablation in 1986 and early 1987 were reviewed with particular reference to the colposcopy findings and cytology results following treatment.

Between 1979 and 1988, nine cases of carcinoma of the cervix have occurred in this unit following laser ablation, five invasive and four microinvasive (Pearson *et al.* 1989). The case records of the five invasive cases were reviewed in this study.

The term abnormal colposcopy includes aceto-white epithelium (AWE), mosaic, punctation, leukoplakia and atypical vessels. An

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'irregular' cervical smear is one showing abnormal cellular changes not amounting to dyskaryosis.

Results

The mean age of the 1000 patients reviewed was 30 years (range 17–57).

The range of histological abnormality preceding laser treatment is summarized in Table 1.

Of the 1000 patients 71 were excluded from analysis because they failed to return for colposcopic assessment after treatment or were reviewed elsewhere. Two were also excluded as they had hysterectomies for menorrhagia before colposcopic and cytological reassessment.

Of the remaining 927 patients available for analysis, 27 have been found to have residual disease giving a cure rate of 97% after 2 years follow-up. Of these 27 women 16 had repeat laser ablation, seven had cone biopsies and four had hysterectomies. The histology of the initial disease treated and that of the residual disease in these 27 patients is summarized in Table 1.

Only six of these 27 patients with residual disease had abnormal colposcopic findings on initial review after laser and five of them also had abnormal cytology. Only one patient, who had residual CIN 1, had abnormal colposcopy with negative cytology. The other 21 patients had normal colposcopic findings at initial review but 16 of them had abnormal cervical cytology. All 16 had abnormal colposcopic findings subsequently, 13 at the next visit and three only on their third colposcopic assessment.

Five patients with residual disease had negative colposcopy and cytology on their first review but had abnormal cytology on their subsequent smear a year later. Abnormal colposcopic findings were noted on review and biopsies confirmed residual or recurrent disease.

Table 1. The distribution of pathology in patients treated by laser and those with residual disease

		Patients with residual disease	
Histology	Patients treated	Initial disease	Residual disease
HPV	149	5	2
CIN1	77	0	4
CIN2	232	2	4
CIN3	542	20	17
Total	1000	27	27

Of the 927 patients colposcoped after laser treatment, 67 had abnormal colposcopic findings and six of them had confirmed residual disease. Thus, colposcopic assessment after laser treatment had a 91% false positive rate.

Abnormal cytology was reported in 134 patients on initial review, of which 21 had residual disease, giving a false positive rate of 85%. However, of the 113 false positive smears 65(58%) were reported as irregular with no evidence of dyskaryosis.

A review of five invasive cancers occurring after 4222 laser treatments in this unit has been reported previously (Pearson *et al.* 1989). One patient who defaulted from follow-up presented with a clinical carcinoma when referred for infertility investigations. Another had a Stage IIIB carcinoma when seen for her first follow-up visit, cytology also being abnormal. The remaining three were detected by abnormal follow-up cytology alone. The longest interval between laser treatment and detection of the invasive lesion was between 5 and 6 years.

Discussion

The treatment of CIN and HPV infection of the cervix using the CO_2 laser results in cure rates in excess of 90%. Because of the occurrence of residual disease and the small risk of developing invasive disease of the cervix (Pearson *et al.* 1989), long-term follow-up is mandatory. This usually consists of initial colposcopy and cytology followed by continued cytology. In the early years of laser treatment when the natural history of patients following laser ablation to the cervix was unknown, colposcopic assessment was more intense. Burke (1982) assessed patients colposcopically and cytologically at 6 and 12 weeks after treatment followed by 6-monthly for 1 year and then annually thereafter. In this unit combined colposcopic and cytological assessment was initially performed at 3 and 6 months, and 1 and 2 years after treatment (Evans & Monaghan 1983).

In recent years there has been a dramatic increase in the number of women with abnormal cytology being referred for colposcopy. With the recent nationwide introduction of the cervical cytology call system the number of referrals will increase even more. Initial colposcopy of these patients combined with any subsequent treatment and review has resulted in a marked increase in the workload of colposcopy units. In our own unit the total number of patients seen in the colposcopy clinics in 1988 was 6711 compared with 4800 in 1984. With this large number of patients, the time available to colposcope each one comprehensively is limited. As no additional information was thought to be gained from repeated colposcopic examination, follow-up in this unit has changed from four colposcopic visits (Evans & Monaghan 1983) to one.

In this study only six of 27 patients (22%) with residual disease were noted to have abnormal colposcopic findings, although 67 (7%) of all patients were deemed to have abnormal colposcopy on initial follow-up after laser treatment. This discrepancy highlights the difficulty in differentiating dysplastic aceto-white epithelium from immature squamous metaplasia occasionally seen after laser ablation.

The 91% false positive rate of colposcopy after laser treatment resulted in a large number of unnecessary cervical biopsies with their attendant morbidity. No patient with invasive disease after laser treatment was detected by colposcopy alone.

Cervical cytology was abnormal in 96% of patients with residual disease giving a far higher detection rate than routine colposcopy. This confirms that cytology alone is adequate for review of patients treated by laser ablation for CIN or HPV infection of the cervix.

As a result of this study routine colposcopic assessment after laser ablation of the cervix is not recommended. We suggest regular cytological follow-up, and colposcopic assessment only after one dyskaryotic or two irregular smears.

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Transvaginal ultrasound in the diagnosis and treatment of tubo-ovarian abscess

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Summary. Transvaginal ultrasound showed tubo-ovarian abscess in 10 patients admitted for acute pelvic inflammatory disease, and transvaginal ultrasound-guided aspiration of tubo-ovarian abscess was performed under antimicrobial treatment. Only light sedation was required and the procedure was well tolerated by the patients. The short-term recovery of all patients was quick and uncomplicated. This new technique is a useful alternative for the diagnosis and treatment of tubo-ovarian abscess.

Tubo-ovarian abscess is a serious sequel of acute pelvic inflammatory disease (PID). The management of the unruptured abscess is still controversial, with recommendations ranging from prompt radical surgery to conservative treatment with intravenous antimicrobials (Landers & Sweet 1983). Recently, laparoscopy has been used with success in the diagnosis and treatment of tubo-ovarian abscesses and pyosalpinx to preserve ovaries and tubes (Henry-Suchet *et al.* 1984; Reich & McGlynn 1987; Teisala *et al.* 1989). We describe the use of transvaginal ultrasound in the diagnosis and treatment of tubo-ovarian abscess.

Patients and methods

The study group consisted of 10 women admitted for severe PID to the Department of Obstetrics and Gynaecology in the University Central Hospital, Tampere, Finland, between February and December 1988. The mean age of the patients was 33 years (range 22–46 years). Four patients were using an intrauterine contraceptive device and six had no contraception. The mean duration of symptoms was 4 days (range 1–14 days). Nine of the 10 patients had fever (>38°C) on admission. Only one patient had a history of previous PID.

On admission, specimens for isolation of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* were obtained from the cervix. Intravenous antimicrobial treatment was started.

A suppository of 10 mg diazepam was given 30 min before transvaginal ultrasound-guided aspiration of the abscess within 48 h after admission. The procedure was undertaken in the dorsal lithotomy position using a Toshiba SAL-77B with a 5-MHz transvaginal probe model PVE-582V (Toshiba Co., Japan), and a sterile needle guide and 16-gauge aspiration needle (Swemed Lab., Sweden) designed for this probe. The probe was covered with a sterile condom and placed in the lateral fornix of the vagina. The abscess was aligned with the needle guide and the needle introduced into the abscess through the vagina. The pus was aspirated using a Craft suction unit (Rocket Co., UK) to the preset vacuum (maximum 600 mmHg) required. Specimens for cytological examination, for iso-

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lation of *C. trachomatis*, *N. gonorrhoeae*, anaerobic and facultative bacteria were obtained from the pus aspirated and handled as described by Heinonen *et al.* (1985).

The response to therapy after aspiration was assessed by clinical examination, transvaginal ultrasound, and C-reactive protein (CRP) which was measured on admission and every 3rd day after aspiration. The mean duration of stay in hospital was 11 days (range 5–18 days). The follow-up time was 1 month.

Results

Clinical examination showed a pelvic mass in only six of the 10 patients in whom transvaginal ultrasound examination revealed a tubo-ovarian abscess. Figure 1 shows a typical image indicating a complex adnexal mass with cystic and solid components. In all patients only one aspiration was performed and the mean volume of pus aspirated was 52 ml. Two patients (nos 1 and 10) had bilateral abscesses, the other eight had a unilateral abscess. *E. coli* was isolated from four patients (Table 1), *C. trachomatis* was isolated from the cervix in one patient, and *N. gonorrhoeae* in none. Cytological examination of the aspirated pus revealed inflammation in all cases without cellular atypia.

The mean decrease in CRP was 72% (range 45–95%) on the 3rd and 90% (range 72–98%) on the 6th day after aspiration. The recovery of all patients was uncomplicated. Transvaginal ultrasound showed a cystic pelvic mass in one patient 1 month after aspiration. The CRP level was below 10 mg/l in all patients.

Discussion

Compared with laparoscopy, clinical examination is not as reliable in the diagnosis of tubo-ovarian abscess (Teisala *et al.* 1989). Spirtos *et al.* (1982) found that in severe PID transabdominal ultrasound confirmed the diagnosis in 94% in comparison with laparoscopy. New transvaginal high-frequency probes afford a higher picture quality and increased potential diagnostic power in the examination of fallopian tubes and ovaries (Timor-Tritsch & Rottem 1987). In this study clinical examination diagnosed an abscess in only six out of 10 cases confirmed by transvaginal ultrasound.

Rupture of a tubo-ovarian abscess is a generally accepted indication for immediate surgical intervention. The management of an unruptured abscess, on the other hand, is controversial. Conservative treatment with antimicrobials and prophylactic drainage, or aspiration of the abscess through a laparoscope is preferred (Henry-Suchet *et al.* 1984; Reich & McGlynn 1987; Teisala *et al.* 1989). Colpotomy drainage of the abscess used to be the more common treatment (Rivlin 1983). Antimicrobial treatment alone may have an impaired response in severe PID involving an abscess, because the bacteria content in the abscess is high and the antimicrobial concentrations are low (Sweet *et al.* 1983).

Table 1. Clinical findings and response to therapy in patients with tubo-ovarian abscess

Patient no.	Volume of aspirated pus (ml)	Micro-organisms isolated from the pus	Initial treatment regimens	C-reactive protein (mg/l) Days after (+) aspiration (0)		
				0	+3	+6
1	120	*Escherichia coli*	C+M*	67	14	8
2	70	*Escherichia coli*	C+M	135	69	38
3	110	*Escherichia coli*	Ci+M	121	67	29
4	40	*Escherichia coli*	D+M	53	8	3
5	10	*Streptococcus α-haemolyticus*	D+M	85	8	3
6	55	*Acinetobacter calcoaceticus*	C+M	104	30	8
7	10	No growth	D+M	83	4	3
8	15	No growth	D+M	154	78	22
9	35	No growth	D+M	86	22	3
10	50	No growth	C+M	93	21	2

* C, Cefuroxim; Ci, ciprofloxacin; D, doxycycline, M, metronidazole.

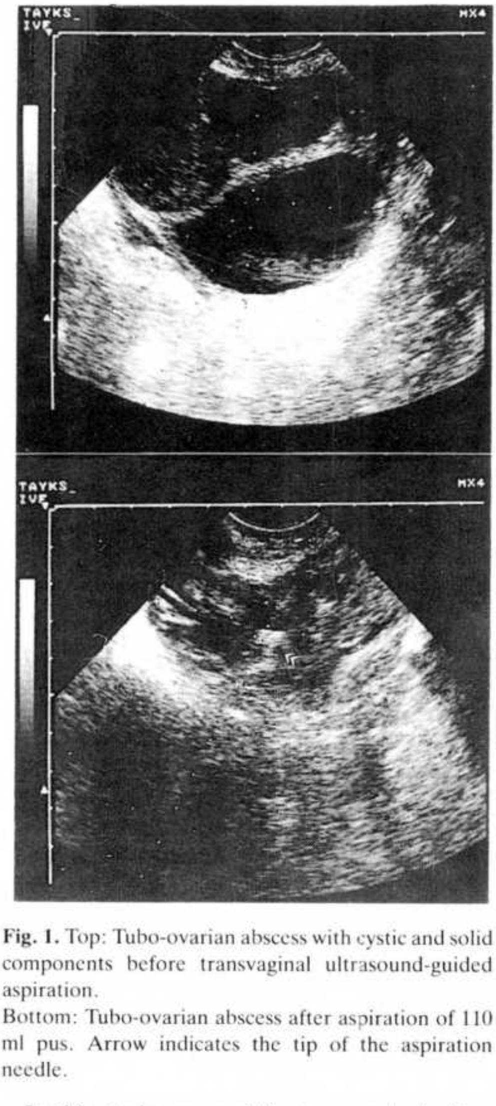

Fig. 1. Top: Tubo-ovarian abscess with cystic and solid components before transvaginal ultrasound-guided aspiration.
Bottom: Tubo-ovarian abscess after aspiration of 110 ml pus. Arrow indicates the tip of the aspiration needle.

In this study we used the transvaginal ultrasound-guided technique designed for oocyte retrieval to aspirate the abscess in 10 patients, with good success. The recovery of the patients was quick and all of them had a good short-term response to therapy. Microbiological findings were positive in 60%. The negative culture results can be explained at least partly by the fact that aspiration was performed under intravenous antimicrobial cover or by failure of transport or culture techniques.

Transvaginal ultrasound-guided aspiration can be performed under light sedation and the procedure was well tolerated by the patients. When general anaesthesia is not required there is less risk for the patient and lower costs. The tubo-ovarian abscess often consists of cystic and solid components. Through transvaginal ultrasound-guided aspiration it is possible to aspirate all cysts of the abscess, which may be difficult at laparoscopy.

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Laser laparoscopy in the treatment of endometriosis. A 5-year study

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Summary. The carbon-dioxide laser used laparoscopically provides a precise and virtually bloodless technique for the vaporization of endometriotic implants in the pelvis. The technique has been used at St Luke's Hospital, Guildford, for the past 6 years and this report presents 228 consecutive patients with endometriosis treated during the 5 years between 1982 and 1987 and followed up for between 1 and 6 years. Pain was improved in 70% and 80% of the 56 infertile patients with endometriosis as the only identifiable abnormality conceived. Of the 54 pregnancies, only 37 (69%) had a successful outcome, reflecting the high pregnancy failure rate found in women with endometriosis. Hospital stay was relatively short and complications were few and usually minor and there was no injury or morbidity caused by laser energy. The main advantage of laser laparoscopy in endometriosis is that patients may be treated at the time of diagnosis with less need for medication and no delay before conception is attempted.

During the past two decades diagnostic laparoscopy has dramatically altered the management of patients presenting with pelvic pain and infertility. Direct inspection of the pelvic organs has allowed a diagnosis to be made and encouraged a more rational approach to treatment. The next logical step was to attempt to correct some of the pathological conditions discovered by operative laparoscopy using specially designed scissors and thermo-coagulators (Semm 1984). These techniques have undoubtedly reduced the need for major surgery in many patients but are, nonetheless, relatively crude. With the increasing sophistication of medical technology the laser has emerged as a surgical tool that can be used endoscopically with a high degree of precision.

The biological effect of the CO_2 laser on tissue is precise vaporization such that, although there is some cellular damage up to 500 μm from the point of impact, the depth of thermal necrosis is usually <100 μm (Bellina *et al.* 1984) Since all the tissue debris is evacuated in the laser plume, there is minimal fibrosis or scar tissue formation and laser wounds heal with virtually no contracture or scar tissue formation (Allen *et al.* 1983). These characteristics make the CO_2 laser particularly suitable for the precise vaporization of endometriosis and its associated adhesions and a valuable tool for endoscopic fertility surgery.

Subjects and methods

All patients admitted from the gynaecology clinic for diagnostic laparoscopy for pelvic pain or infertility, or both, were asked to consent to laser treatment at the same time if endometriosis or associated adhesions were discovered. The operating theatre staff were always ready with

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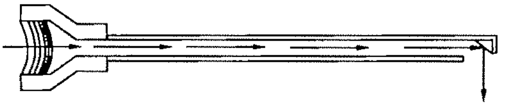
the necessary equipment if it was decided to proceed to operative laser laparoscopy.

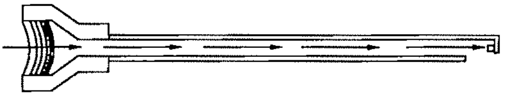
A 35 W Sharplan 733 CO_2 laser generator was used with a TEM 00 mode. Laser energy was transmitted via a fixed mirror and lens with a focal length of 200 mm through a hollow second puncture probe inserted in such a way that the laser beam was as near as possible to a 90° angle of incidence to the tissue to be vaporized. The spot size was 0·45–0·50 mm when the laser beam was precisely focused 20 cm beyond the end of the delivery probe. A modification of this probe with a non-reflective backstop to prevent ongoing transmission of the laser beam was used whenever adhesions had to be divided. A third probe with an inbuilt mirror set at 45° to the direction of the beam was used for the vaporization of endometrial deposits in otherwise inaccessible positions such as the back of the broad ligament or the ovarian fossa. These probes are illustrated in Fig. 1.

A third puncture suction and irrigation probe was inserted supra-pubically in the mid-line to irrigate the lasered areas and remove as much charcoal as possible and to provide intermittent suction to remove excess irrigating fluid and the smoke that accumulates from the vaporization of tissue. A large amount of smoke was generated during these procedures and to assist in dispersal the CO_2 inflow on the insufflator was maintained on high flow throughout the procedure and the outer smoke evacuation channel was kept open to assist in venting the laser plume.

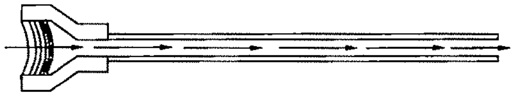
A standard 11 mm laparoscope, coupled to a video camera by a beam-splitter, was used for observation. The operations were all performed by one surgeon (C.S.) and the procedures were recorded with a Sony Trinitron video camera on a Sony U-matic recorder on ¾ inch video tape. The operations were viewed simultaneously on a television monitor to enable the assistant to provide effective help for the retraction and irrigation of tissues by the third portal probe.



Probe with 45° mirror



Probe with back-stop



Probe—open

Fig. 1. Probes used for laser laparoscopy

Results

During the past 6 years 475 patients have been treated by operative laparoscopy using the CO_2 laser for a variety of conditions (Sutton 1986). This report concerns 228 consecutive patients with endometriosis, 216 of whom have now been followed up for intervals between 1 and 6 years; the other 12 women were treated but have been lost to follow-up. Fifty-four patients were treated as day cases, 166 stayed overnight, 7 stayed for 48 h, and only one required 5 days in hospital.

The women were classified according to the symptom treated: 159 women had pelvic pain, usually associated with congestive dysmenorrhoea and deep dyspareunia; a further 28 had pelvic pain and infertility; and 41 had infertility alone. The results are tabulated diagramatically in Table 1.

Of the 187 women with pelvic pain 181 were interviewed and examined 3 months and 1 year after the operation, 126 (70%) were pain free or the symptoms were improved to such an extent that they were no longer troubled by them. In 38 patients the operation had not alleviated their symptoms, and a further 17 were initially better but the symptoms returned, usually after about 6 months.

The 69 women with infertility were followed up for varying lengths between 6 months and 6 years after the laser procedure. Only six women were lost to follow-up and four of these had moved to other countries. Of the remaining 63 women, 38 had primary and 25 secondary infertility. Their ages ranged from 18 to 37 years and the duration of infertility from 6 months to 10

Table 1. Interval between laser laparoscopy and pregnancy in 45 women

Procedure-to-pregnancy interval (months)	No of pregnancies (%)
0–8	33 (73)
8–12	7 (16)
12–16	4 (9)
>18	1 (2)

Table 2. Severity of endometriosis related to rate of pregnancy in 63 women with infertility*

Severity of endometriosis	No. followed up	No. with other factors for infertility*	Pregnancies n (%)
Minimal	19	3	15/16 (94)
Mild	26	1	17/25 (68)
Moderate	16	3	11/13 (85)
Severe	2	0	2/2 (100)
Total	63	7	45/56 (80)

* Other factors included oligospermia in six and cervical fibroids in one, leaving 56 patients with endometriosis as the only factor.

years. Six women had partners with low sperm counts ($<15 \times 10^6$/ml) and one patient had a large cervical fibroid causing gross distortion of the cervical canal but refused to have a myomectomy to correct this problem.

The remaining 56 patients had endometriosis as the only abnormal factor implicated in their infertility. All were ovulating normally and had husbands with a normal sperm profile and post-coital tests within the normal range. Of these 56 women, 45 (80%) have become pregnant at varying intervals after laser laparoscopic treatment of endometriosis. Most of them (73%) became pregnant within 8 months of laser treatment. The procedure–pregnancy interval and the relation of the outcome to the severity of endometriosis are shown in Tables 2 and 3.

Seven of the 45 patients who became pregnant had been on danazol or buserelin at varying intervals before the laser laparoscopy and most had been referred from other hospitals for laser treatment. Only two women with a successful outcome were given anti-endometriosis drugs after laser laparoscopy and these had both failed to conceive during the year following the procedure. Four of the 11 patients who did not conceive were referred for in-vitro fertilization, although none has conceived at the time of writing.

Of the 45 patients who achieved a pregnancy, nine conceived twice, and these 54 pregnancies ended in 11 miscarriages, one neonatal death at 28 weeks and 37 livebirths (including one set of twins). Five pregnancies were terminated, four for social reasons and one which was found to have reduced amniotic fluid volume at 16 weeks and cordocentesis revealed triploidy. Since intrauterine death was inevitable the patient elected to have a termination of pregnancy. The actual 'take home' baby rate was therefore only 69%.

Discussion

Although pelvic endometriosis may be suspected on clinical grounds the actual diagnosis and assessment of severity can only be made at the time of laparoscopy (Booker 1988). There is considerable controversy over the relation between the milder forms of endometriosis and infertility and it has been suggested that the finding of minimal or mild endometriosis during infertility investigation may be casual rather than causal (Lilford & Dalton 1987). On the other hand, the severity of the pain seems to bear little relation to the extent of the disease found at laparoscopy, and recent research has shown that patients with mild disease can produce more prostaglandin F and experience more pain than those with severe disease (Vernon *et al.* 1986).

Sometimes it may be reasonable to withhold treatment, but Thomas & Cooke (1987) have shown that the untreated condition can progress so the clinician may be criticized if complications develop at a later date. Most drugs used to treat endometriosis cause biochemical disturbances (Fahreus *et al.* 1984; Booker *et al.* 1986; Meldrum *et al.* 1982) and unpleasant side-effects (Jelly 1987). Furthermore the risk of teratogenic

Table 3. Results of laser laparoscopy for endometriosis

Authors	No. of patients	Pregnancies n (%)
Daniell (1985)	40	20 (50)
Feste (1985)	29	21 (72)
Davis (1986)	65	37 (57)
Nezhat *et al.* (1986)	102	62 (61)
Donnez (1987)	70	40 (57)
Feste (1989)*	64	52 (81)
Present study*	56	45 (80)

* Endometriosis alone, no other infertility factors

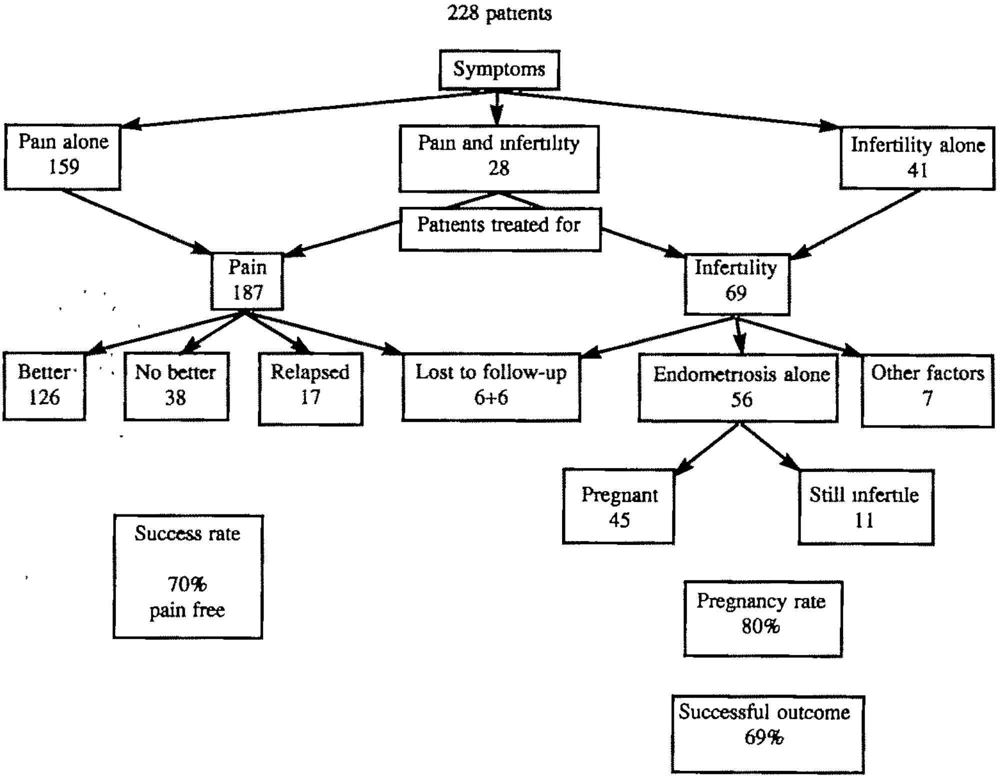


Fig. 2. Results of laser laparoscopy in patients with endometriosis.

effects means that pregnancy should be avoided during the 6–9 months of treatment which is difficult for someone anxious to start a family. Laser laparoscopy offers the considerable advantage of definitive treatment at the time of diagnosis thus allowing conception to be attempted without delay.

The first reports on laser laparoscopy came from Clermont-Ferrand, France (Bruhat *et al.* 1979) but prototype instruments and techniques were developed independently in Israel (Tadir *et al.* 1981), United States (Daniell & Brown 1982), UK (Sutton 1986) and Belgium (Donnez 1987). All the original investigators have shown that the technique is safe in the hands of an experienced operative laparoscopist and the complication rate is low. None of our patients had any problems from the intraperitoneal use of laser energy.

Our data compare favourably with results from the USA (Daniell 1985; Feste 1985; Davis 1986; Nehzat *et al.* 1986) and Europe (Donnez 1987). Nezhat *et al.* (1986) obtained 62 pregnancies in 102 patients which included one elective termination and nine miscarriages. This high rate of miscarriage (15%) is reflected in our series although unfortunately our rate is even higher (20%). This phenomenon is almost certainly unrelated to laser surgery and reflects an increased rate of miscarriage noted among endometriosis sufferers. In a recent review, Malinak & Wheeler (1985) have reported levels as high as 31–49% in women with endometriosis. The results of several recent studies are shown in Fig. 2.

Most of the published reports on laser laparoscopic surgery in the treatment of endometriosis have dealt exclusively with infertility where the outcome is easy to quantify. However, most women with endometriosis present with pelvic pain, dysmenorrhoea and dyspareunia, and because these symptoms are so subjective the results are less easy to analyse. Since we were essentially treating the symptoms rather than the diseases we merely recorded the patient's interpretation of whether her symptoms had improved, remained the same or deteriorated since the laser treatment. This approach and the retrospective nature of this study are open to criticism and we are about to embark on a double-blind prospective study which we hope will provide more meaningful information. All that we can claim at this time is that laser laparoscopic surgery appears to be safe in expert hands and the results appear to be promising. The main advantage of laser laparoscopy is that it allows effective treatment at the same time as the diagnosis is made, with less need for operative surgery or expensive drugs, many of which have unpleasant physical and biochemical side-effects.

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Listeriosis revisited: the role of the obstetrician

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Summary. The clinical course and outcome is described of three pregnancies complicated by listeriosis encountered during a 6-month period. All three ended in preterm labour characterized by the passage of meconium by the fetus. Two babies died in the early neonatal period and the third survived with neurological handicap. Although the diagnosis of listeriosis was made only after delivery, all the mothers had a pyrexial illness before delivery. A high index of suspicion is needed for the early detection and prompt treatment of this life-threatening perinatal infection. Effective advice concerning prevention of listeriosis by avoidance of high-risk foods must be given to women during pregnancy.

Listeria monocytogenes has been recognized as an infectious agent in man since 1929 (Nyfeldt 1929). However, it has gained prominence in recent years with a marked increase in reported cases (McLauchlin *et al.* 1988; Goulet *et al.* 1986) since last reported in this journal (Khong *et al.* 1986). The Department of Health issued a food hazard warning in February 1989 with reference to unpasteurized milk, soft cheeses, cook-chill foods and prepacked salads. This has been aimed at those groups in whom *Listeria* causes symptomatic infection, especially immunosuppressed patients, pregnant women and newborn infants. Three babies with perinatal listeriosis are reported and ways in which the diagnosis could have been made earlier and listeriosis possibly prevented are discussed.

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Case reports

Patient 1

A 36-year-old woman in her second pregnancy was well until 32 weeks gestation when she developed a flu-like illness for 2 days followed by a perception of reduced fetal movements. She was admitted having had irregular uterine contractions for 6 h. Examination was unremarkable and the uterine cervix was closed. The cardiotocographic trace was reactive, with irregular uterine activity. Eight hours after admission the membranes ruptured spontaneously with the release of meconium-stained amniotic fluid. The fetal heart record showed prolonged baseline bradycardia and she was delivered by caesarean section. The mother's postoperative recovery was uneventful.

L. monocytogenes was cultured from a high vaginal swab. In retrospect the mother remembered having eaten a soft French cheese 9 days before delivery and consuming a prepacked bean-sprout salad purchased at the local supermarket 2 days before the illness.

The male infant weighed 2·040 kg and was born in poor condition with Apgar scores of 2, 6 and 8 at 1, 5 and 10 min respectively.

After intubation and suction of blood and meconium from below the vocal cords he was ventilated and transferred to the intensive care unit. Gram-positive rods were identified in the gastric aspirate and he was treated with intravenous amoxicillin and gentamicin. Subsequent blood cultures and cerebrospinal fluid cultures grew. *L. monocytogenes.*

Over the next 3 weeks he continued to require ventilation and he remained on antibiotics. Chest radiography revealed bilateral pneumonic changes. Generalized seizures developed at 12 h of age requiring anticonvulsant therapy. Intraventricular haemorrhages were noted on cranial ultrasound and progressive ventricular dilatation was initially managed medically but subsequently required a ventriculo-peritoneal shunt. Clinical features of hepatitis became obvious by the 4th day of life with liver function returning to normal at the time of hospital discharge at 8 weeks. Subsequent development has been impaired and at 8 months he showed early signs of spastic diplegia and truncal hypotonia.

Patient 2

A 35-year-old primigravida was transferred to our hospital at 29 weeks gestation in preterm labour. The pregnancy had been normal until 12 h before admission when she had developed a febrile illness and painful uterine contractions ensued. On admission, her temperature was 37·8°C. The fetal heart-rate tracing showed a baseline rate of 180 beats/min and shallow decelerations. Labour was rapid with concurrent deterioration of the heart-rate tracing before vaginal delivery. After delivery the maternal pyrexia settled during the next 24 h. Vaginal swabs were negative. In retrospect the mother remembered consuming cold, precooked chicken during the last trimester.

The baby girl weighed 1420 g. She was in poor condition at birth with Apgar scores of 2, 4 and 7 at 1, 5 and 6 min respectively and intubation and high-pressure ventilation were required. Gram-positive rods were identified in the gastric aspirate and she was treated with intravenous amoxicillin and gentamicin *L. monocytogenes* was later grown from the gastric aspirate, blood cultures and skin surface swabs.

Over the following 3 days the baby required increasing ventilatory support. Chest radiography showed bilateral opaque lung fields with early interstitial emphysema. Hypotension was corrected with infusions of dopamine and dobutamine and a double volume exchange blood transfusion was performed because of septicaemia. On the 3rd day cranial ultrasonography revealed bilateral intraventricular haemorrhages. On the 4th day she became persistently hypoxic in 100% oxygen and did not respond to a prostacycline infusion, an EEG showed long periods of electrical silence with short bursts of highly bizarre activity, and further support was discontinued. She died later that day.

Post-mortem examination showed she had bilateral intraventricular haemorrhages with extension into the cerebral tissues. Microscopic examination of lung, liver and adrenal glands showed occasional microabscesses/granulomas, a histological appearance entirely in keeping with the diagnosis of congenital listeriosis (Larroche 1977; Fox 1978).

Patient 3

A 28-year-old primigravida had had umbilical sepsis at the age of 7 days followed by the later development of oesophageal varices secondary to portal hypertension which eventually required decompression with a lieno–renal shunt and splenectomy, oesophageal transection and sclerotherapy. Her present pregnancy had been uneventful with no medication other than supplementary iron and folate. At 33 weeks gestation she had a flu-like illness which resolved spontaneously but recurred 7 days later. On admission her temperature was 38·7°C but with no cause apparent on general examination. The uterus was soft and the cervix closed. The white cell count was $38{\cdot}7 \times 10^3$/l with 88% granulocytes. There were a few red cells and pus cells in the urine and a presumptive diagnosis of urinary tract infection was made and she was treated with oral cefadroxil. The fetal heart had a baseline rate of 180 beats/min and a baseline variability of 10 beats/min. After 6 h the baseline variability was reduced to 5 beats/min and there were shallow unprovoked decelerations. Twenty-one hours after admission the membranes ruptured spontaneously with the release of meconium-stained amniotic fluid. She was delivered by caesarean section.

Over the next 36 h the mother received antibiotics and the pyrexia settled. In restrospect, she remembered having eaten large amounts of a variety of soft cheeses purchased from a supermarket in France 3 weeks before the birth.

The male infant had a birthweight of 2·532 kg. He was in extremely poor condition at birth with Apgar scores of 2 at 1, 5 and 10 min and 4 at

20 min. Copious green-stained, purulent material was sucked from the oropharynx and trachea during direct laryngoscopy before intubation. Despite high-pressure ventilation, chest expansion remained poor and the heart rate remained below 100/min even after the administration of adrenalin via the endotracheal tube. An arterial blood gas analysis showed a persistent, severe mixed respiratory and metabolic acidosis. This failed to respond to infusions of sodium bicarbonate and tris-hydroxymethyl-aminomethane (THAM). Further ventilatory support was discontinued at 3 h.

Subsequent blood cultures, gastric aspirate and placental swabs grew *L. monocytogenes*.

At post-mortem the lungs were a deep purple, congested, consolidated and contained pus in the airways. The liver also showed deep congestion but no focal lesions. The meninges were congested and covered by an exudate. Histologically, there were numerous microabscesses/granulomas in the lungs, liver, adrenal glands and thymus and meninges. The placenta weighed 567 g and measured 19 × 14 × 2 cm. Microscopic examination showed acute chorioamnionitis, villitis, funisitis and numerous microabscesses/granulomas, characteristic of congenital listeriosis (Larroche 1977; Fox 1978). *L. monocytogenes* was cultured from specimens of lung.

Discussion

Reports of confirmed *L. monocytogenes* infections returned to the Public Health Laboratory, Communicable Disease Surveillance Centre, have recently increased sharply; 1965–1977 saw an average of fewer than 50 cases per annum. This increased to between 115 and 150 cases per annum during the years 1983–1985. In 1986, 137 cases were confirmed; this nearly doubled in 1987 to a total of 259 cases (Hall *et al.* 1988). The figure for 1988 is 291 cases, 93 of which were perinatal. The population incidence is estimated at 4·3 cases per million with an estimated perinatal case rate of about 1 in 9700 births (McLauchlin *et al.* 1988). Our patients represent 1 in less than 1000 births. Listeriosis would appear to be more common in France where the population incidence has recently been estimated to have risen from 3·27 in the 1970s to 11·3 per million in 1984 (Goulet *et al.* 1986). The marked increase would appear to be not only the result of increased awareness and reporting, as it has been associated with a disproportionate increase in a specific serotype (strain 4b) (Hall *et al.* 1988). This serotype is the main cause of perinatal infection, accounting for between 33% (Schwartz *et al.* 1988) and 90% (Schlech *et al.* 1983) with mortality rates of 32% (Linnan *et al.* 1988) to 47% (Schlech *et al.* 1983). *Listeria* is ubiquitous and is found in soil, the faeces of asymptomatic individuals, vegetables, and animal feed, and it is likely that most of us are colonized by and excrete the organism for short periods following ingestion of contaminated food. However, colonization manifests as listeriosis only in susceptible individuals such as the immunocompromised, the newborn, the elderly, and occasionally pregnant women where the organism has a predilection for the placenta and membranes.

The foods that have been identified as the most likely source of infection include dairy produce (Linnan *et al.* 1988; *Bulletin* 1988; Bannister 1987; Fleming *et al.* 1985), vegetables (Schlech *et al.* 1983), meat, poultry (Schwartz *et al.* 1988), and shellfish (Lennon *et al.* 1984). Up to 80% of poultry carcasses may be contaminated with *Listeria* organisms which are also present in the environment of meat preparation plants. Pasteurization of dairy products may not eradicate *Listeria* (Fleming *et al.* 1985; Pini & Gilbert 1988) and the organism itself thrives at a temperature of 4°C, the temperature of most refrigerators. This issue presents a considerable challenge to those involved in food preparation (Kerr & Lacey 1988).

In our three patients the fetus was alive on admission, all three had had a pyrexial illness before delivery and, on rupture of the membranes, there was meconium staining of the amniotic fluid. Meconium passage is very unusual before 34 weeks gestation but has been reported to be a sign of fetal infection with *Listeria*. In all three women the fetal heart rate trace was abnormal. *Listeria* can be difficult to isolate and the presenting signs and symptoms of listeriosis are non-specific. However, prompt diagnosis may enable successful maternal treatment with ampicillin or amoxicillin, thus avoiding congenital infection (Hume 1976; Linnan *et al.* 1988; Evans *et al.* 1985).

It is important to consider listeriosis as a possible cause of an unexplained pyrexial illness in pregnancy, particularly if the amniotic fluid is meconium stained, and not the more common diagnosis of urinary infection. Appropriate investigations include Gram staining and bacterial culture of vaginal swabs. Blood should be taken for cultures before antibiotic therapy. After delivery the placenta should be examined whenever congenital infection is suspected. In addition to Gram staining and culture of surface swabs, frozen sections of the placenta could enable a rapid diagnosis.

All our three patients had eaten foods that carry a risk of contamination with *Listeria*. Whilst we were not able to prove these foods were the source of infection, a history of consumption of soft cheeses, cook-chill chicken eaten cold or incompletely reheated, or prepacked salads is suggestive. Pregnant women must be given constructive advice about foods which might be dangerous in pregnancy. The inoculation dose of *Listeria* which will cause infection is not known (Editorial 1989) and therefore any contamination with *Listeria* in food is undesirable. Uncooked and undercooked meat, including poultry, should be avoided. Recently certain types of pâté have been found to be infected. These should, therefore, be avoided. Precooked meals that have subsequently been stored at refrigeration temperatures (cook-chill method) should be thoroughly recooked before eating. Dairy products, in particular those derived from unpasteurized milk, and raw vegetables which have been stored cool after preparation (e.g. coleslaw) should be avoided. Unlike most food poisoning organisms, *Listeria* can multiply at temperatures found in cool storage cabinets and domestic refrigerators. It is particularly important that vigilance is maintained whilst travelling abroad. The common habit of buying cheeses in continental Europe and then travelling back to Britain without using any form of refrigerated container is dangerous. *Listeria* thrive under these conditions.

The restrictions so placed on the eating habits of pregnant women should not prevent them from eating varied and nutritious diets. We feel that all antenatal clinics in the UK should offer specific dietary advice in leaflet form on avoidance of those foods implicated in the transmission of *Listeria*.

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Endometrial hyperplasia in an oophorectomized woman receiving tamoxifen therapy. Case report

SIMON S. CROSS, SEZGIN M. ISMAIL

Case report

A 54-year-old woman with uterine bleeding was admitted for a hysterectomy. She had had a mastectomy for breast carcinoma 13 years earlier, followed 9 years later by bilateral oophorectomy when metastatic breast carcinoma was identified in axillary nodes. Two years before this admission she was treated with tamoxifen 20 mg twice daily which was reduced to 20 mg daily 6 months later. She was continuing tamoxifen therapy at this dose at the time of admission. On admission her oestradiol was 42 pmol/l (normal postmenopausal levels <250 pmol/l). No residual ovarian tissue was identified during the hysterectomy procedure.

Pathological findings

Macroscopic appearances. The uterus measured 9 × 6 × 4 cm and contained an intracavity polypoid lesion 3 cm in length. A few intramural tumours with a whorled cut surface, up to 1 cm in diameter, were seen.

Microscopic appearances. The background endometrium was composed predominantly of dilated weakly proliferative glands in an inactive fibrotic stroma. Within the polyp there was considerable architectural distortion of the endometrial glands some of which showed cystic dilatation while others showed budding and branching (Fig. 1a). Many of the glands within the polyp were lined by epithelial cells showing nuclear pleomorphism, nuclear crowding and many mitotic figures (Fig. 1b). In contrast the stroma within the polyp was inactive and fibrotic. No evidence of invasive malignancy was seen. The intramural tumours were confirmed as leiomyomas.

Discussion

The pathological diagnosis of endometrial hyperplasia is made on the microscopic finding of morphologically abnormal proliferative-type endometrium (Kurman & Norris 1987); some authors insist that in addition there must be an abnormal increase in endometrial volume (Hendrickson & Kempson 1980). The diagnosis of endometrial hyperplasia in this oophorectomized patient was based on the microscopic finding of endometrial glands showing marked proliferative activity, architectural disarray and cytological atypia, combined with the macroscopic observation of a 3 cm endometrial polyp. Endometrial hyperplasia implies prolonged oestrogenic stimulation of the endometrium unopposed by progesterone (Hendrickson & Kempson 1980). It is therefore surprising to find endometrial hyperplasia in an oophorectomized woman receiving an anti-oestrogen, tamoxifen.

Tamoxifen acts by binding to the 17 β-oestradiol receptor. Although initially it may exert an oestrogen-like effect, the tamoxifen-receptor complex shows long-term nuclear retention so that prolonged oestrogen antagonism follows the early oestrogenic manifestations (Neumannova *et al.* 1985). Little information is available on the endometrial effects of long-term tamoxifen therapy. Sherman *et al.* (1979) assessed the effects, on five healthy premenopausal women, of tamoxifen 20 mg daily continued only for two

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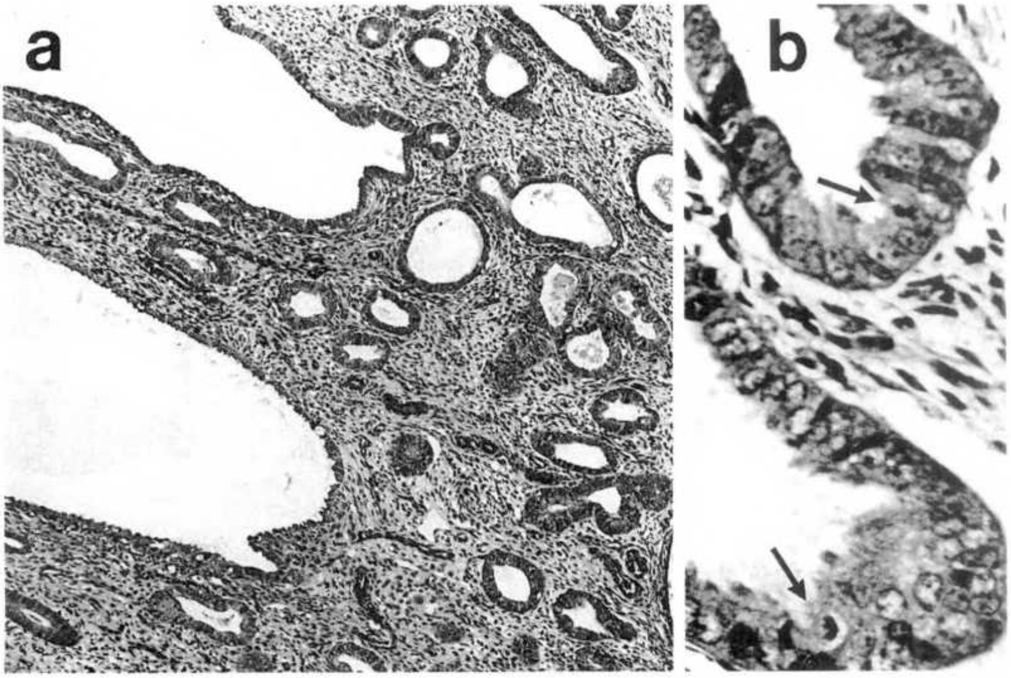

Fig. 1. (a) Low power view of endometrial polyp showing distorted glandular structures of varying sizes in a spindly stroma. × 65 Haematoxylin and eosin. (b) Endometrial glands showing nuclear crowding and pleomorphism with mitotic figures (arrowed). × 400 Haematoxylin and eosin.

or three cycles. They found no morphological alterations in the endometrium during the proliferative phase of the menstrual cycle but there was a marked deficiency of the changes associated with progesterone during the luteal phase. We have been unable to find any systematic studies of the effect of tamoxifen on postmenopausal endometrium.

The occurrence of endometrial hyperplasia in this instance may be explained in several ways.

The endometrium may have been subject to oestrogenic stimulation. It has been suggested that tamoxifen may act directly on the ovary to stimulate oestradiol release without intermediary gonadotrophin stimulation (Groom & Griffiths 1976; Sherman *et al.* 1979). This mechanism cannot account for the endometrial hyperplasia in our patient because she had been oophorectomized and there was no evidence of residual ovarian tissue at operation nor at histological examination. The observation that this patient's oestradiol level on admission was within the postmenopausal range is evidence against the presence of a non-ovarian endogenous or exogenous oestrogen source.

The early oestrogen-like effects of tamoxifen are unlikely to be relevant as our patient had been receiving tamoxifen for 2 years. However, the tamoxifen-receptor complex may exert a persistent low-grade oestrogen-like activity, the cumulative effect of which in long-term tamoxifen therapy could result in endometrial hyperplasia. Boccardo *et al.* (1981) have described an oestrogen-like action of tamoxifen on vaginal epithelium which becomes apparent after 4 weeks of therapy but which may decline after 24–48 weeks of continuous treatment.

Tamoxifen may have a direct action on endometrial proliferation which is not mediated via the oestrogen receptor.

There is an increased occurrence of endometrial carcinoma in association with breast cancer, and the atypical endometrial hyperplasia in our patient may merely have represented the early stages of endometrial carcinoma in a genetically predisposed individual. However, the finding of atypical endometrial hyperplasia in this tamoxifen-treated woman cannot be dismissed lightly in view of two reports of a possible tamoxifen-induced increase in the occurrence of endometrial carcinoma. Killackey *et al.* (1985) reported endometrial carcinoma in three women treated with tamoxifen for breast cancer, two of whom were postmenopausal; they considered that the frequency of endometrial carcinoma in their tamoxifen-treated breast cancer patients was higher than would be expected among breast cancer patients treated by other means. Fornander *et al.* (1989) also showed a significant increase in the frequency of endometrial carcinoma in postmenopausal women treated for breast cancer with tamoxifen. Of the 931 women treated with tamoxifen 13 developed endometrial carcinoma whereas none of the 915 women in the control group did so. The cumulative frequency of endometrial carcinoma was significantly greater in patients who continued tamoxifen therapy for longer than 2 years.

The occurrence of endometrial hyperplasia with focal cytological atypia in our patient and the reports of an increased occurrence of endometrial carcinoma raise interesting parallels with oestrogen-associated endometrial carcinomas where malignancy occurs on a background of hyperplasia. We therefore postulate that tamoxifen exerts its effects on the endometrium via the oestrogen receptor and that it has a long-term low-grade oestrogen-like effect. The progesterone antagonism observed by Sherman *et al.* (1979) in their study of the endometrial effects of tamoxifen in premenopausal women may also be relevant in the development of tamoxifen-associated endometrial hyperplasia and neoplasia.

Further studies of endometrial morphology in subjects receiving long-term tamoxifen therapy would be useful and may help further elucidate the mechanisms of endometrial proliferation.

Acknowledgment

We thank Professor B. Hibbard for permission to publish this case report.

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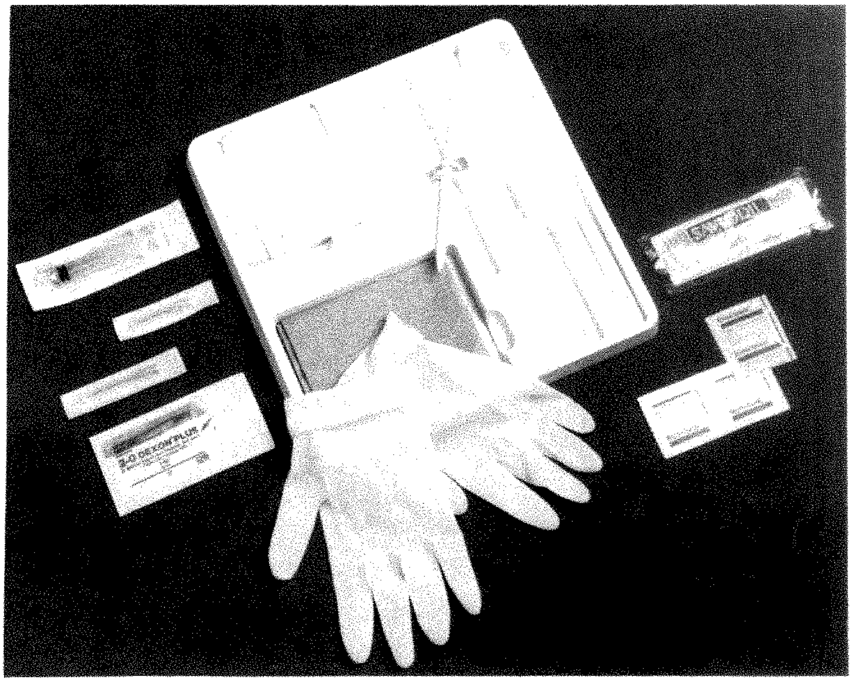

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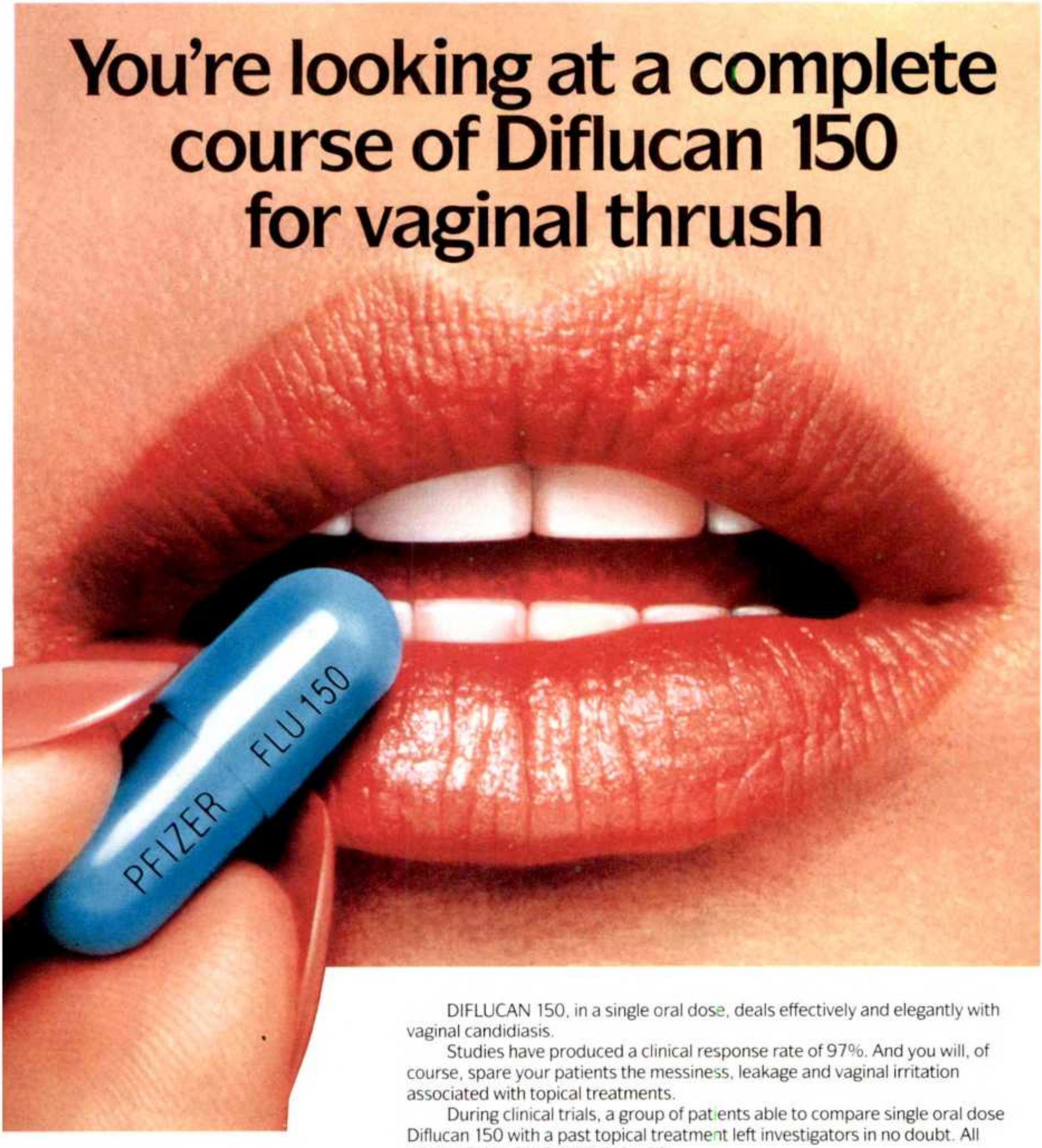

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British Journal of Obstetrics and Gynaecology
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CORRESPONDENCE

Ligneous conjunctivitis involving the cervix. Case report

Dear Sir,

Readers may be interested to know the outcome of treatment in the case of oculo-oro-genital ligneous disease reported by Rubin *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 1228–1230].

Treatment was commenced with twice-daily vaginal applications of 10% hydrocortisone acetate in a mucoadherent foam (Colifoam). This produced a dramatic reduction in vaginal discharge and improvement in dysmenorrhoea as measured by days off work each month. Ligneous material remained on the cervix but in reduced amount. This improvement was maintained by once-daily applications, but not by twice-daily applications containing 1% hydrocortisone acetate (Proctofoam HC).

Reports of the response to specific therapy such as hyaluronidase, alpha-chymotrypsin, fibrinolysin, streptokinase, plasminogen activator and heparin are mixed and unconvincing. We feel that this patient's response is probably non-specific and related to reduction in the inflammatory component. The converse has certainly been reported, i.e. exacerbation of the condition following trauma, infection or surgery. Repeated biopsies of the cervix almost certainly contributed to the severity of the condition. Greater familiarity with this condition would enable early diagnosis from the characteristic histology.

The patient has recently started treatment for infertility probably caused by the diseased cervix. We can find no reports of the effects of pregnancy on this condition.

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Reference

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Outcome of labour in occipitoposterior positions in an African population

Dear Sir,

It is regrettable that the short report by N. D. Briggs [*Br J Obstet Gynaecol* (1989) **96**, 1234] did not indicate whether a partograph was used in the mangement of labour. There is ample evidence (Philpott 1972; World Health Organization 1988) that efficient use of partography allows timely recognition of prolonged labour regardless of the rotation of the fetal head. Appropriate timing of transfer, augmentation, or intervention in labour can thus be achieved. The more widespread adoption of partographic management of labour incorporating 'action' and 'alert' lines must be a higher, cheaper and more appropriate priority throughout the world, but perhaps particularly in Africa, than expecting all labours to be supervised by a person capable of recognizing early occipito-posterior positions.

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Polycystic ovarian disease (PCOD) and non-insulin-dependent diabetes mellitus (NIDDM)

Dear Sir,

Gjonnaess [*Br J Obstet Gynaecol* (1989) **96**, 714–719] found an increased prevalence of gestational diabetes in 89 anovulatory women with PCOD successfully treated by ovarian electrocautery, and suggested that obesity was the responsible factor. Leedman and colleagues [*Br J Obstet Gynaecol* (1989) **96**, 1095–1098], discussing a case of ovarian hyperthecosis, a variant of PCOD (Nagamani *et al.* 1981), in association with NIDDM, indicated that insulin resistance is thought to be the primary defect in PCOD and hyperthecosis (Chang & Geffner 1985; Nagamani *et al.* 1986). Perhaps to some extent they are both correct.

I have studied fasting insulin levels and the family histories of 50 oligoamenorrhoeic women with PCOD and 50 regularly menstruating women with normal ovarian morphology. The fasting insulin range for the control group had an upper limit of 14 m-units/l (mean +2 SD). Of the 50 women with PCOD, 29 (58%) had fasting insulin concentrations above this value. The obese PCOD patients (n=27) had higher mean fasting insulin levels than the non-obese (n=23) (27·2 *vs* 14·3 m-units/l; Mann–Whitney test, U=171, P=0·004) but the non-obese patients differed significantly from 43 non-obese controls (5·7 m-units/l; Mann–Whitney test, U=220,P<0·001). Of the 50 women with PCOD 16 (32%) had a family history of NIDDM compared with only six of the 50 (12%) controls (χ^2=5·83, d.f.=1, P<0·02>0·01).

These data show that fasting hyperinsulinaemia is a common feature of PCOD. Although the abnormality is influenced by body-weight, it is not primarily related to obesity, and the strong family history of NIDDM amongst blood relatives points to a familial trait.

In a large proportion of patients with PCOD the underlying defect seems to be insulin resistance, itself the result of a genetically determined abnormality of the insulin receptor (Kahn *et al.* 1976). Euglycaemia is maintained in early life by a compensatory rise in insulin levels but during pregnancy, when insulin resistance rises, or in late adult life, when the pancreas fails to compensate, the predisposition to diabetes is revealed. Obesity, also by elevating insulin resistance (Barbieri & Ryan 1983), further increases the tendency to NIDDM in these women.

The prognosis for women with infertility related to PCOD is good, even those with severe forms are now being treated successfully (Fleming *et al.* 1985). Such patients form a readily identifiable at-risk group suitable for pre-pregnancy dietary advice and antenatal screening for gestational diabetes.

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A total of 250 136 laparoscopic sterilizations by a single operator

Dear Sir,

I feel constrained to comment on the work undertaken by Dr P. V. Mehta between January

1979 and September 1988 [*Br J Obstet Gynaecol* (1989) **96**, 1024–1034].

On 8 March 1988, Mr J. Guillebaud and I observed Dr Mehta performing 148 sterilizations in under 5 h with absolutely amazing surgical skill. However, at the end of the day, it was patently obvious that no medical records whatsoever of these 148 procedures were maintained. The only brief documentation was the pre-procedure data of the subject, made by non-medical clerical assistants, for the purpose of record of payments made to these subjects.

The mortality figures confirmed by the Joint Secretary of the Government of West Bengal [Guillebaud's commentary, *Br J Obstet Gynaecol* (1989) **96**, 1019–1021] pertain to Dr Mehta's work in the state of West Bengal, not in other states in India where work was done earlier. In general, the standard of record-keeping in India can be appalling, and, consequently, in such a survey, the question of reliability must arise.

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Guillebaud J. (1989) Mass laparoscopic sterilizations. *Br J Obstet Gynaecol* **96**, 1019-1021.

Mehta P. V. (1989) A total of 250 136 laparoscopic sterilizations by a single operator. *Br J Obstet Gynaecol* **96**, 1024-1034.

Author's reply

Dear Sir,
In response to Dr Bhathena, I present the following comments.

At each camp one of the paramedical staff notes down on a sheet of paper any abnormal findings or immediate operative complications narrated by the operating surgeon with the name and the serial number of the patient. At the end of the camp the findings are recorded in the register at the primary health centre and the same information is handed over to the surgeon to complete his record. On 8 March 1988 there were no abnormal findings or immediate operative complications, as has been already mentioned in the commentary by Guillebaud (1989). Hence no special procedure notes were made. This might have been misunderstood as absence of medical records of the procedure.

The statement made by the Joint Secretary of West Bengal regarding *ex gratia* financial payment of 10 000 rupees, quoted by Guillebaud (1989), stands true for all the states of India, and hence the mortality figures from other states have the same authenticity as in West Bengal.

I agree that data collection presents a problem, as stated in my paper 'the data derived from this part of the study should nevertheless be interpreted with caution'.

I hope this satisfies your enquiry.

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BOOK REVIEWS

Neurology of Pregnancy Second edition by James O. Donaldson. W. B. Saunders Co., London, 1989, 347 pages with figures and tables, £35.00

Every obstetrician and neurologist should possess or have immediate access to this excellent book. It is well written and is easy and enjoyable to read. The wisdom of the author and his wide experience shine through the clear text. It is comprehensive with only one major omission: the problems of HIV infection and acquired immune deficiency syndrome are not covered. The only other quibbles are minor ones: the references have been updated for this new edition, but even so they are marginally thin on recent entries; the section on neurological complications of regional anaesthesia is rather short for this important practical topic; and the index could be improved for the next edition. *Neurology of Pregnancy* is an invaluable text which will prove useful to students and doctors in training as well as established specialists. It will also be readily digestible by midwives, curious about neurological problems that have developed in their patients.

D. J. Thomas

Prenatal Diagnosis in Obstetric Practice edited by M. J. Whittle & J. M. Connor. Blackwell Scientific Publications, Oxford, 1989, 274 pages with figures and tables, £29.50

I believe that this book is the first attempt to give practising obstetricians a concise yet wide-ranging account of all aspects of prenatal diagnosis.

The pace of advance in the field has been such in recent years that there is a need for an updated source for easy reference. The editors, perceiving this need, have used the expertise of their immediate colleagues in a variety of disciplines to produce what is effectively a series of articles. Despite the large number of contributors the editors have maintained a similar format for each of the chapters with well-arranged and numbered tables and figures. Inevitably some of the ultrasound pictures have not reproduced as clearly and, despite the individual explanatory notes, some additional side-by-side sketches would be welcome, bearing in mind that not all who read this book will be used to interpreting some of the less usual anatomical ultrasound views.

The references in the chapters are sensibly kept to a minimum as there are appendices to most giving a list of further reading as well as the excellent list at the end of the book of the disorders amenable to prenatal diagnosis. Each of these four appendices describes the main diagnostic method used, i.e. ultrasound, biochemical analysis, DNA analysis or other methods.

The contributors resist the temptation to advance a didactic approach to the various problems and their views are eminently sensible and uncontroversial.

This excellent book fills a real gap and will be a success. The idea behind it has been well thought through and then equally well delivered. I believe that Whittle and Connor will soon be required to update their data for another edition as their book will undoubtedly become an everyday reference for all those involved in the field.

R. H. T. Ward

Human Papillomavirus and Cervical Cancer (IARC Scientific Publications No. 94) edited by N. Mũnoz, F. X. Bosch & O. M. Jensen. Oxford University Press, Oxford, 1989, 155 pages with figures and tables, £19.00

The field of HPV research is rapidly evolving and this review is a timely reminder that the causal association between HPV infection and cervical neoplasia is far from proven. This is the report of a meeting held in March 1988 in Copenhagen to discuss the epidemiology of cervical neoplasia and HPV infection, and the conclusions from this meeting precede the main text. The first chapter is an excellent review of the epidemiology of cervical cancer and highlights the strengths and weaknesses of many original papers. The areas covered not only include sexual factors but also smoking, contraception, immunosuppression and non-HPV infection.

Subsequent chapters deal with HPV infection from a clinical perspective and describe the results of genital HPV infection using the techniques currently available to the gynaecologist and cytopathologist. However, these techniques are generally of poor specificity and sensitivity and additionally show considerable inter-observer error.

The value for many clinicians will be the chapters dealing with the molecular biology of these viruses. The methods of detecting HPV-DNA are concisely described and will not overburden the reader. The advantages and disadvantages of each technique are summarized and, although these techniques are now widely used, their specificity and sensitivity have never been fully assessed. Because of recent advances relating to the oncogenic potential of HPV and the possible mechanisms by which this is achieved the chapter dealing with this area is now slightly dated.

I recommend this review to both those seeking an introduction to this topic and also those involved in this area of research for the excellent chapters on the epidemiology of cervical cancer and HPV infection.

John Tidy

Human Sexuality and its Problems by John Bancroft. Churchill Livingstone, Edinburgh, 1989, 748 pages, 125 illustrations, £24.95

John Bancroft's second edition of *Human Sexuality and its Problems* has built on the excellent material of the first edition. It updates the reader with current research and thinking, including the implications of HIV and AIDS.

In the introduction Bancroft makes a personal statement about his own attitudes and values in relation to human sexuality. This courageous and challenging start to the book invites the reader to be aware of his or her own attitudes and values. It also opens up the wide variety of issues to consider while acknowledging the current limitations of our understanding.

This book will be of immense value to anyone working in the field of obstetrics and gynaecology, both as a reference book and for reading in its entirety. As before, it covers the whole field of human sexuality from the knowledge foundation of the biological basis of human sexuality through to classifying sexual problems and reviewing different therapeutic approaches. There are 13 chapters in all and each one ends with a comprehensive list of references. Chapter 12 on sexual aspects of fertility, fertility control and infertility is of particular relevance.

I recommend this book, for to quote Bancroft's first sentence, 'the thread of sexuality is woven densely into the fabric of human existence'.

Fran Reader

Pathology of the Uterine Cervix, Vagina and Vulva (Vol. 21 in the series Major Problems in Pathology) edited by Yao S. Fu & James W. Reagan. W. B. Saunders Co., Philadelphia, London, 1989, 397 pages with figures and tables, £43.00

This is a thorough account of the normal tissues and a comprehensive review of the pathological processes which occur in the vulva, vagina and cervix, including descriptions of many rare pathological processes. It is extensively illustrated, and the illustrations are of a very high quality. It has, as the authors state, been written for both pathologists and gynaecologists and to a major extent it achieves this aim.

I particularly liked the chapter on infectious and inflammatory diseases and the one on the handling of tissues. There is a great deal of good advice in this latter chapter.

The sections on intraepithelial neoplasia are, however, disappointing, confusing and lack clarity because the authors combine a mixture of older and modern terms in order, I suppose, to satisfy users of both systems. They will, as a consequence, satisfy neither. The explanatory, introductory, sections do not overcome the confusion in the later text because many readers do not read chapters in continuity, selecting only the portions relevant to their immediate needs

The nature of this confusion can be gauged from the fact that in a chapter which uses the terms mild and moderate dysplasia, the section on the treatment and prognosis of cervical intraepithelial neoplasia refers only to the treatment of CIN. Are we to assume, therefore, that, as the authors use CIN to mean only severe dysplasia and carcinoma *in situ,* that treatment of CIN I and II is not required?

The authors have missed the opportunity to update the nomenclature of vulval epithelial disorders and use the 1976 classification of vulval dystrophy and terms such as 'Bowen's dysplasia' and 'carcinoma *in situ*' of the vulval skin when many UK readers would prefer vulvar intraepithelial neoplasia (VIN).

These problems considerably reduce the value of the book and deter me from recommending it.

C. H. Buckley

Books received some of which may be reviewed at a later date

Ovarian Cancer. Biological and Therapeutic Challenges edited by F. Sharp, W. P. Mason & R. E. Leake. Chapman and Hall Ltd, London, 1990, 480 pages fully illustrated, £65.00

Aids in Gynecology (Clinical Practice of Gynecology, Volume 1 No. 1) edited by Newton G. Osborne. Elsevier, New York, 1989, 144 pages with figures and tables, $35

Baillières Clinical Obstetrics and Gynaecology. Dysfunctional Uterine Bleeding and Menorrhagia. Volume 3/Number 2, June 1989, edited by J. O. Drife. Baillière Tindall, London, 428 pages. UK annual subscription £40, single issue £18.50

Oxford Reviews of Reproductive Biology Volume II 1989 edited by S. R. Milligan. Oxford University Press, Oxford, 449 pages with figures and tables, £45.00

Turner Syndrome edited by Ron G. Rosenfeld & Melvin M. Grumbach. Marcel Dekker, Inc., New York, 1990, 552 pages with figures and tables, $150 (US and Canada), $180.00 (all other countries)

Legal Principles and Practice in Obstetrics and Gynecology Volume 1 edited by Max Borten & Emanuel A. Friedman. Year Book Medical Publishers, Inc., Chicago, 1989, 338 pages, £38.50

Acyclovir Therapy for Herpesvirus Infections edited by David A. Baker. Marcel Dekker, Inc., New York, 1990, 334 pages, fully illustrated, $99.75 (US and Canada), $119.50 (all other countries)

Benign Disorders and Diseases of the Breast: Concepts and Clinical Management by L. E. Hughes, R. E. Mansel & D. J. T. Webster. Baillière Tindall, London, 1989, 212 pages fully illustrated with colour plates, £39.50

The New Our Bodies and Ourselves The Boston Women's Health Book Collective. British edition by Angela Phillips & Jill Rakusen. Penguin Books, 1989, 716 pages illustrated, £12.99, soft cover

Menopause by Derek Llewllyn-Jones & Suzanne Abraham. Penguin Paperback, London, 1988, 146 pages, illustrated, £4.50

Incontinence by R. C. L. Feneley, J. G. Malone Lee & S. L. R. Stanton. A Family Doctor Booklet published by the British Medical Association, BMA House, Tavistock Square, London, 1989, 48 pages, illustrated, £1.20 (plus 20p postage if ordered)

Feminism and Epistemology: Approaches to Research in Women and Politics (Women and Politics Vol. 7 No. 3) edited by Maria J. Falco. Haworth Press, Inc., Binghamton, New York, 1988, 127 pages, £22.95

Proceedings and Symposia

Menopause: Evaluation, Treatment, and Health Concerns (Progress in Clinical and Biological Research Volume 320) Proceedings of a National Institute of Health Symposium held in Bethesda, Maryland, in 1988, edited by Charles B. Hammond, Florence P. Haseltine & Isaac Schiff. Alan R. Liss, New York, 1989, 339 pages, $96.00

Intrauterine Growth Retardation Nestlé Nutrition Workshop Series Volume 18 edited by Jacques Senterre. Raven Press, New York, 1989, 332 pages with figures and tables, $57.00

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COMMENTARIES

Hysteroscopic alternatives to hysterectomy

Many thousands of hysterectomies are performed each year in women who have menorrhagia resistant to medical treatment but who have no demonstrable uterine abnormality.

It has long been a goal of gynaecologists to avoid major surgery in such women, but early attempts at local destruction of the endometrium with corrosive chemicals and destructive physical agents were unsuccessful because of the amazing capacity of the endometrium to regenerate (Goldrath & Fuller 1985). It is necessary to destroy the basal layers of the endometrium completely to prevent the endometrium repairing itself in the same manner as it would after being shed physiologically at menstruation.

Recent advances in hysteroscopic equipment permit easy and rapid inspection of the entire uterine cavity. In addition to permitting more precise diagnoses to be made, hysteroscopy allows the endometrium to be treated selectively under direct vision (Gordon & Lewis 1988; Baggish *et al.* 1989). Two techniques using this approach are currently attracting considerable interest. The full thickness of the endometrium may be ablated using a Nd-YAG laser or resected using an electro-surgical resectoscope.

Goldrath *et al.* (1981) described a technique of direct-view hysteroscopic ablation of the endometrium with the Nd-YAG laser. The main advantage of this technique derives from the property of Nd-YAG laser energy to be widely scattered in tissue and so to produce relatively deep tissue coagulation necrosis. This destruction extends down through the endometrium for about 5 mm, which ensures adequate destruction of the basal layers of the endometrium whilst being safely contained within the 20 mm thickness of the myometrium (Masterson 1985). These properties make uterine perforation and haemorrhage unlikely. Several studies (Staehler *et al.* 1981; Goldrath 1985*b*, Davis 1987) have shown only minimal temperature changes on the serosal surface of the uterus after Nd-YAG laser application to the endometrial surface, so there is only a small risk of thermal damage to surrounding structures. Keiditsch *et al.* (1981) demonstrated that the necrosis produced by the Nd-YAG laser was reproducible and sharply delineated in contrast to the irregular and unpredictable necrosis produced by electrosurgical energy, thus the Nd-YAG laser was superior to electrocoagulation as a means of destroying tissue whilst preserving the structure of the bladder wall.

Goldrath (1989) reported his 10-year experience with this laser ablation technique; he obtained an overall success rate of 96% and noted that recurrence of menorrhagia was very rare. Six publications (Goldrath 1985*b*; Danniell *et al.* 1986; Loffer 1987; Lomano 1988; Baggish & Baltoyannis 1988; Davis 1989) and four presentations at international meetings (Bertrand 1989, Grochmal 1989; Erian 1989, Garry 1989) have reported a total of 696 patients treated with the Nd-YAG laser, 577 (83%) of whom obtained excellent relief with complete amenorrhoea in 58% and only slight vaginal staining for a day or two in the remainder. A further 65 women continued to have regular but very light menstruation which they considered a satisfactory result. Only 46 (7%) were considered to be treatment failures.

These results from centres in the USA and the UK are encouraging but as with any surgical procedure there are also complications and dangers An inevitable consequence of any surgery to the endometrium is disruption of the subepithelial capillary plexuses with resultant vascular absorption of the distending medium. Fluid overload and pulmonary oedema may occur (Goldrath 1985*b*; Morrison *et al.* 1989) and great care must be taken with the monitoring of fluid balance. The other potential operative problems are uterine perforation, haemorrhage, and thermal damage to surrounding structures. Goldrath

(1985*b*) reported one perforation but this was associated with insertion of the hysteroscope and was not a consequence of the laser treatment. Haematometra occurred in seven of Goldrath's early procedures, and Davis (1989) reported one intrauterine infection. There were no other major complications reported in any of these series. Perhaps the main source of danger remains the inexpert use of the equipment. Two fatalities have been described in the USA caused by the inappropriate use of CO_2 rather than fluid as the intrauterine distending medium.

The main disadvantage of endometrial laser ablation is the very high capital costs of the equipment. There has therefore been considerable recent interest in the much cheaper endoscopic alternative of electrosurgical resection using techniques and equipment very similar to those used by urologists for transurethral resection of the prostate. The procedure was first described by DeCherney & Polan (1983) for use in patients with intractable uterine bleeding in whom hysterectomy was contraindicated. Subsequently 21 further women were treated in this way and all but one of those who survived their presenting illness became amenorrhoeic (Decherney *et al.* 1987). A technique of 'partial resection' has been developed in Europe to 'normalize' menstrual losses, and this appears to be successful, but numerical data are not yet available (Hamou 1989). Magos *et al.* (1989) described endometrial resection as an alternative to hysterectomy in women with menorrhagia Six of 11 women who had total resection became amenorrhoeic, four had lighter periods and one had a solitary episode of bleeding a few weeks after the treatment. These results appear to be similar to those achieved with the much more expensive laser therapy.

If the results of the two procedures turn out to be similar will the complications rate also remain comparable? Endometrial resection with electrosurgical energy requires the uterus to be distended with a non-electrolytic and hence non-physiological medium. Excess systemic absorption of a solution such as glycine risks the development of dilutional hyponatraemia. This progressive syndrome, well known to urologists, can be serious and difficult to treat and may result in impairment of consciousness, coma and even death (Emmett *et al.* 1969; Sellevold *et al.* 1983; McLucas 1989*b*; Blanc *et al.* 1989). Endometrial resection also requires the surgical removal of the whole of the endometrium. Removal of too little will result in inadequate treatment whilst removal of too much will threaten both the major blood vessels and the integrity of the uterine wall. In skilled hands endometrial resection can be an elegant and effective technique but in less skilled hands there appears to be a significant risk of uterine perforation and damage to structures outside the uterus. DeCherney *et al.* (1987) became so concerned about these potential risks that he does not recommend resection in women fit for hysterectomy, and cautions that if such operations are undertaken that simultaneous laparoscopy be performed to minimize these risks. In Europe three fatalities have occurred in the last 12 months following endometrial resection (Hamou 1989) and I have been informed of four uterine perforations associated with this technique in the UK, one of which was associated with serious blood vessel and ureteric damage.

Other intrauterine techniques are also being developed. Considerable interest in the USA is being shown in 'rollerball' ablation (Vancaille 1989; McLucas 1989*a*). The roller is a 2 mm sphere on an electrosurgical resectoscope wire which can roll freely around its axis. A unipolar coagulating current is applied to the endometrium and this produces a zone of coagulation necrosis similar to that produced by the Nd-YAG laser. Preliminary results with this technique are encouraging, as are those produced by a novel idea being developed in Watford which utilizes a microwave principle to destroy the endometrium.

The potential benefits of selective endometrial destruction as an alternative to hysterectomy are enormous. Women who are treated successfully are frequently delighted with the short hospital stay and minimal convalescent time. Many also appreciate the option of retaining their uterus whilst losing their symptoms. Health authorities and private insurance companies are also very interested in a technique which clearly offers a new procedure which is not only popular and effective but also offers the opportunity to make substantial financial savings. Equipment manufacturers also sense a potential dramatic increase in their markets and are therefore understandably keen to actively promote the techniques.

Gynaecologists are therefore finding themselves under increasing consumer, administrative and commercial pressure to become involved in the development of endometrial ablative procedures. Caution, however, is clearly essential here. Competent hysteroscopy is essential to these procedures. Although many gynaecologists have performed an occasional hysteroscopy, very few use the technique regularly and even fewer have heeded the pioneering advice given by Gordon and Lewis (1988) that the traditional dilatation and curettage should be replaced by hysteroscopy and curettage. No urologist would be tempted to perform a transurethral resection without a considerable familiarity with all aspects of cystoscopy. It is essential that gynaecologists similarly do not attempt endometrial surgery until they are competent hysteroscopists.

The relative effectiveness, safety, and true costs of each of these procedures are not yet established. It is important that each technique is fully assessed before it is introduced into routine practice. Those currently assessing the procedures should collaborate and set up a joint research programme and agree common selection criteria, common data collection protocols and devise standard treatment outcome measures. Above all they should co-ordinate the collection of adverse outcomes and complications so that we can determine which if any of the procedures should be introduced into general clinical practice. These are exciting times in gynaecological surgery. Any advance which threatens the pre-eminence of gynaecology's two most commonly performed operations—dilatation and curettage, and hysterectomy—must be considered important. We must, however, be certain that what we introduce is indeed an improvement on current practice and we can only ensure this by carefully evaluating both the old and the new procedures with correctly structured, collaborative, prospective, clinical studies.

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Cytological terminology

The cervical smear report should convey accurate information clearly and concisely so that it is easily understood by all medical practitioners who take smears, most of whom do not have specialized knowledge of pathology or gynaecology. The classification of cytology smears introduced by Papanicolaou (1954) was used by most cytologists in the early days of gynaecological cytology but its broad categories do not reflect current concepts of cervical pathology. As a result subsidiary classifications have evolved sporadically, engendering confusion. They have not only precluded comparisons between centres but have also invited misinterpretation and the possibility of inappropriate management of women with abnormal cervical cytology.

To rectify this situation The British Society for Clinical Cytology (BSCC) has twice published recommendations on terminology for use in reporting gynaecological cytopathology (Spriggs *et al.* 1978; Evans *et al.* 1986). The recommendations of the 1986 publication were endorsed in the report of the Intercollegiate Working Party on Cervical Cytology Screening (1987) and incorporated in the revised cervical smear request form (HMR 101/5 (1989)).

The BSCC recommendations are based on use of the cytological term dyskaryosis to describe abnormal cells compatible with origin from cervical intraepithelial neoplasia (CIN) or carcinoma of the cervix. Dyskaryosis, literally 'abnormal nucleus', is classified into mild, moderate and severe according to appearances suggesting origin from CIN 1, CIN 2 and CIN 3 or invasive carcinoma. It is acknowledged that distinction between the cytological appearance of human papillomavirus (HPV) and mild dyskaryosis of CIN 1 cannot always be made reliably and also that severe dyskaryosis may be accompanied by additional features which suggest but are not always diagnostic of an invasive tumour.

The BSCC working party considered the use of cytological terms both scientifically correct for description of individual cells seen with the microscope and easily understood if confined to a small and clearly defined vocabulary Prediction of the histology may be included but only as a subsidiary statement because colposcopically directed biopsies have shown that the relation between the milder degrees of cellular abnormality in particular and the histological condition is less close than had been assumed before (Singer *et al.* 1984; Soutter *et al.* 1986; Walker *et al.* 1986; Giles *et al.* 1988). The abnormal smear report should conclude with a recommendation for the further management of the patient.

Recently a Workshop of American experts convened at the National Institutes of Health in Bethesda, Maryland, by the Division of Cancer prevention and Control, National Cancer Institute has made further recommendations for cytology reporting to replace the Papanicolaou classification. The most interesting component of this 1988 Bethesda System (National Cancer Institute Workshop 1989) is its division of smears showing cytological evidence of CIN or HPV into just two categories, high-grade and low-grade *squamous intraepithelial lesions* (SIL). Low-grade SIL includes cell changes associated with HPV and with CIN 1 whereas high-grade SIL encompasses CIN 2 and CIN 3. They classify squamous cell carcinoma separately Division of CIN into two histological categories instead of three is supported by recent reports of poor agreement between histopathologists in the diagnosis of CIN 1 (and of CIN 2 to a lesser extent) from cervical biopsies (Ismail *et al.* 1989, Robertson *et al.* 1989).

Unfortunately, the Bethesda System for reporting cervical cytology has disadvantages which outweigh potential benefit. It employs histological terms, which have been defined for description of tissue, for reporting cellular material. This practice has been rejected by BSCC working parties as scientifically incorrect and possibly misleading. For example, the separate classification of invasive cancer and squamous intraepithelial lesions in the Bethesda System implies that these conditions can be reliably distinguished from a smear, which they cannot.

The Bethesda System recommends that the cytology report comments on smear quality and advises that it should be categorized as 'satisfactory for interpretation', 'less than optimal' or 'unsatisfactory'. Microscopic criteria of a reliable smear are controversial, illustrating the difficulty and uncertainty surrounding the problem. The introduction of a 'less than optimal' category may satisfy the microscopist but would be difficult to accommodate in a population screening programme.

Further problems are encountered in cervical cytology with the equivocal or borderline smear. A continuous range of nuclear changes occurs from those associated with inflammation, which are regarded as benign, through more striking abnormalities that are associated with CIN and invasive cancer. Although there are distinct morphological differences between simple inflammatory changes and the dyskaryosis of CIN, there are a small number of smears in which the distinction is not clearly manifest. These smears are classified as borderline on the new Department of Health cervical smear request form (HMR 101/5 (1989)), meaning on the borderline between inflammation and mild dyskaryosis. Well women with borderline smears require a further smear to resolve the problem unless they have suspicious clinical signs or symptoms, when they should be referred immediately for colposcopy. If a well woman has two borderline smears she should be referred for colposcopy. The Bethesda System calls this borderline smear *atypical squamous cells of undetermined significance*. The phrase describes the problem aptly but the propensity for abbreviation to atypical or atypia, words which have been applied to diverse cytological abnormalities over the years, led the BSCC working party to reject it for *borderline*.

The Bethesda System is being recommended to editors of medical journals worldwide with the advice that the Papanicolaou numerical classification should be replaced by a descriptive terminology. A descriptive terminology is already well established in the British cervical screening programmes. Data can be converted easily from the British terminology to the Bethesda System if necessary. However, the British terminology is well founded. Its use has improved standards of reporting and achieved comparability between centres as well as providing a basis for external quality assessment. It should continue to be used.

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Early pregnancy tests

The time when a new human life begins has been the subject of much philosophical deliberation, debate and disagreement The start of pregnancy is a less contentious issue, but an equally difficult concept (Jones *et al.*, 1983). Pregnancy may be defined as the time when one or more potential offspring are attached to the lining of the uterus. The conceptual problem arises from the initial development of a fertilized ovum into a pre-embryo, the lack of a practical reference point for inplantation, leading to the possibility of a pre-pregnancy pregnancy, and the difficulty of assessing embryo viability. Early pregnancy is a vague term that is often used to describe the period between the presumed time of implantation and the end of the 6th week from the last menses. Pregnancy tests based upon the measurement of human chorionic gonadotrophin (hCG) in plasma or urine seek to identify the presence of trophoblastic cells, whereas pelvic ultrasonography can be used to inspect fetal fluids or tissues. Recently both techniques have been improved for alternative or complementary use (Batzer *et al.*, 1983; Nyberg *et al.*, 1988). Rapid tests for hCG have been developed to be used near the subject in the clinic or self-use in the home, while transabdominal or transvaginal ultrasonography can be used to date an early embryo, and screen for abnormalities.

Conception can only occur for a limited and usually unknown period within each ovarian cycle. Accordingly, obstetricians often date an early pregnancy in completed weeks from the 1st day of the last menstrual period (LMP). Unfortunately, even in women with regular menstrual cycles, the time from day 1 of menses to ovulation can vary from 12 to 25 days (Schiphorst *et al.*, 1985). Moreover, intermenstrual bleeding can sometimes be mistaken for menstruation, and ovulation may precede the return of menses after amenorrhea. Defined biochemical or morphological indices of ovulation (Collins 1985) are potentially more accurate reference points for the first stages of pregnancy. Currently, these events cannot be accurately dated in calendar days due to uncertainty about the time of ovulation, and the fact that tests are rarely applied at midnight. Attempts have been made to detect fertilization by the measurement of an early pregnancy factor (EPF) in maternal serum (Mesrogli *et al.*, 1988), but the assay is technically difficult. For practical purposes, the day of the LH peak, or the day of follicular rupture can be designated day 0 for dating a natural pregnancy in the knowledge that fertilization will occur within the next 48 h due to the limited lifespan of the ovum (Royston 1982). The pre-embryo will usually enter the uterus as a morula (16-cell stage) about 5 days after follicular rupture. Similarly the day of hCG administration, or the day of follicular rupture, can be used to date a pregnancy after assisted conception. After *in-vitro* fertilization the embryos are usually transferred to the uterus at the 2–4-cell stage, which is reached 2 days after oocyte collection. Implantation of a blastocyst is thought to start 7–9 days after follicular rupture when the endometrium is becoming thicker due to formation of the decidua and changes in vascularity (Lichtig *et al.*, 1988). There is a significant increase in the concentration of hCG in the maternal circulation (i.e. >50 iu/l) by day 12 after follicular rupture in all cycles that result in a normal pregnancy. This time may precede the development of the amnion, yolk sac and primitive streak by a few days. Fetal heart motion is detectable between the 3rd and 4th completed weeks after follicular rupture (Riddle 1988; Timor-Tritsch *et al.*, 1988).

There are many reasons why tests are used to detect the presence and location of early trophoblastic and embryonic tissue. A woman who wants a baby, or those people responsible for her health management, may use the information to start prenatal care (Lippman *et al.*, 1988), which may include screening for a multiple intrauterine pregnancy. The same tests may be used to detect an anembryonic gestation, a retained dead embryo (Pridjian & Moawad 1989), or an intrauterine haematoma (Mandruzzato *et al.*, 1989). In addition, tubal and even ectopic pregnancies at other sites may be detected (Newton 1988; Mattox *et al.*, 1989). The tests are also used to diagnose and monitor the treatment of trophoblastic tumours. A rapid test result will help a woman with an unwanted pregnancy to take the option of having it terminated by a relatively simple and safe procedure. Early miscarriages may be recognized and monitored (Little 1988; Sweeney *et al.*, 1988). An analysis of all published data showed that the miscarriages rate depended on the stage of pregnancy at which the test was applied, and there was no significant difference in the proportion of failed pregnancies established after natural or assisted conception (Steer *et al*, 1989) These findings are relevant for the diagnosis of disorders with a lower prevalence, and for the assessment of new screening procedures.

The diagnosis of pregnancy was based originally on a combination of physiological signs and symptoms, which included missed menstrual periods, early morning sickness, breast tenderness and a gain in weight. The era of objective testing started about 60 years ago with the development of bioassays for urinary hCG. The first immunochemical tests for hCG were reported about 30 years ago and involved the use of erythrocytes to monitor the binding reactions in a tube and subsequently on a glass slide. These and related procedures could detect about 1000 iu of hCG/1 and would give a reliable test result 6 weeks after the last menstrual period. More sensitive and specific radioimmunoassays (detection limit about 50 iu/l) and later different types of immunometricassay (detection limit about 25 iu/l) were developed for the measurement of the hormone in plasma or urine (see review by Fletcher 1986). The availability of alternative, non-radioactive labels (gold sol particles, enzymes, dye complexes) also enabled the production of stable self-contained immunoassays for urinary hCG (detection limit about 100 iul), and other tests that involved the use of a dipstick coated with an antibody to capture the antigen (detection limit about 50 iu/1). The advent of procedures for immunoconcentration and immunochromatography to enhance the antigen/antibody reactions enabled the production of rapid assays in the form of immunopads and self-contained immunostrips (see review by

Collins 1988). Most early pregnancy tests are performed on site (i.e. near the subject) either by professional persons involved in health care, or by women in their own homes. To date, the simplest selftest for pregnancy involves the use of an immunostrip that contains an integrated wick for sampling from a stream of urine (May 1989).

All tests for hCG that are available commercially have an accuracy >95% when applied to samples from women who are unequivocally pregnant or non-pregnant. The end-point of the test that is indicative of pregnancy is selected on the basis that the number of false-positive results will be <1%. The earliest time that each test can be applied is usually described in terms of the missed menstrual period. It is known, however, that the time from the day of the LH peak or follicular rupture to the day of next menses minus 1 can vary from 10 to 18 days (Schiphorst *et al.*, 1985). Accordingly, more information is required about the detection rates and false-positive rates of commercial tests in relation to less variable reference points. In practice, a test should be repeated if there is any doubt about the result because the concentration of hCG in serum usually doubles every 1·4 to 2·0 days. Women with a positive result from a self-test should be encouraged to seek clinical advice immediately. The potential value of measuring the concentration of other placental proteins during early pregnancy (particularly SP1 after assisted conception) has been assessed (Grudzinskas *et al.*, 1986).

During the last decade developments in pelvic ultrasonography have made an increasing contribution to the diagnosis of early pregnancy. The initial studies were undertaken with trans-abdominal sector scanners utilizing 3.5 MHz transducers. A full, but not overdistended bladder, was required to examine the decidua and measure the volume of a gestational sac. This approach showed the presence of an echogenic area within a darkened and thickened decidua as early as day 11 after follicular rupture (Yeh *et al.*, 1986), and an initial evaluation of the test gave a detection rate of 92% with no false-positive results. A gestational sac could be identified on day 12 and was invariably present at week 4 in normal pregnancies (Riddle 1988). The fetal heart was always identified by week 5. The advent of intravaginal probes utilizing high-frequency ultrasound (up to 7.5 MHz) has produced clearer images of early pregnancies. This approach can detect a gestational sac >2 mm diameter (Bernaschek *et al.*, 1988; Goldstein *et al.*, 1988) by the 5th menstrual week, or around the 21st day after follicular rupture (Timor-Tritsch *et al.*, 1988; Fossum *et al.*, 1988), i.e. about 10 days after the best immunochemical tests for hCG give a positive result. Transvaginal ultrasonography can also be used to monitor the formation of a yolk sac (Yeh & Rabinowitz 1988; Tumor-Tritsch *et al.*, 1988) and the sequential appearance of other embryonic structures (Timor-Tritsch *et al.*, 1988; Warren *et al.* 1989). Fetal heart motion invariably occurs by week 4 during a normal pregnancy.

New tests for the detection and investigation of early pregnancy are usually assessed by comparison with methods already in use (Bree *et al.* 1989). This process enables the identification of defined end-points for each technique. Due to the error in dating a pregnancy, and biological differences in the rate of embryogenesis, it is only possible to be precise about the latest time that a test result is relevant. In practice many tests may have to be repeated to achieve a definitive diagnosis. More information about the prevalence and natural histories of the disorders associated with early pregnancy will enable the techniques to be used more efficiently and effectively. Undoubtedly the tests will also be improved. Professional and self-tests for hCG will continue to become more sensitive, rapid and accurate. The resolving power of transvaginal ultrasonography will be increased, and the development of transcervical probes utilizing higher frequency ultrasound could theoretically enable the detection of an implanted blastocyst (0.1 to 0.2 mm diameter). The recent development of transvaginal colour flow imaging which involves the use of low intensity untrasound will allow a visual inspection of neovascularization in the decidua and developing embryo. Clinical algorithms must be devised for the most suitable way to apply these complementary tests to different populations of women.

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Pregnancy and exercise—exercise and pregnancy. A short review

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Most of the important questions and uncertainties related to pregnancy and exercise can be reduced to two basic questions. First, in what ways does exercise during pregnancy influence the course of pregnancy and the development of the growing fetus? And second, in what ways does pregnancy itself alter the ability to exercise?

Pregnancy and exercise

Exercise is today an integral part of normal life for many women. During pregnancy, many do not want to interrupt their usual routine, some not even when it involves high performance and competitive sport. A result is that we have increasing experience and medical knowledge about pregnancy and exercise and, unavoidably, also about exercise and pregnancy. There are now several systematic prospective studies as well as numerous anecdotal observations on record (Bruser 1968; Jarrett & Spellacy 1983; Kulpa *et al* 1987; Sibley *et al.* 1981; Veille *et al* 1985; Wallace & Engstrom 1987), enough to allow a relatively certain statement: moderate exercise on a regular basis during pregnancy is likely to lead to an improved course of pregnancy when compared with that of a sedentary lifestyle; such exercise is also without notable health hazards to the woman or her fetus providing that she is in good general health and has no pregnancy-related disease.

Exercises and sports which have proved to be very beneficial involve rhythmic motion of large groups of muscles, are aerobic, and do not require delicate balance. Experience has shown that such activities can maintain or even improve physical fitness (Collings *et al.* 1983; Dressendorfer 1978, Erkkola 1976*a*). Subjectively, this is considered an advantage during the stress caused by pregnancy and labour and has been confirmed objectively (Erkkola 1976*b*; Erkkola & Rauramo 1976). Being able to maintain good bodily control and the pleasure derived from active participation also work positively on the emotional state; exercise also aids in preventing certain typical pregnancy disorders such as backache, leg cramps, swollen legs, and varicose veins (Taylor & Pernoll 1987).

The limitations imposed by pregnancy on exercise and sport activity are considered in relation to fetal and maternal risks. These result from physiological changes caused by the intensity of the activity and from dangers specifically related to certain types of exercise and sport.

Maternal trauma-preterm labour

Both direct and indirect consequences of maternal injury are hazardous. The risk of sport injuries might be increased during pregnancy due to changes in the centre of gravity, shape of the body, posture, and softening of ligaments. This is one reason, along with increase in weight, why certain activities such as riding, surfing, water-skiing, team and contact sports should be discouraged. Theoretically, the fear of preterm labour is also justified; strenuous physical activity stimulates increased production of norepinephrine (Artal 1986; Rauramo *et al.* 1982), which has been shown to prompt contractions via alpha receptors in the uterine smooth muscles (Zuspan *et al.* 1962). However, observations during pregnancy in very active athletes

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do not indicate that this mechanism is of any particular significance (Zaharieva 1972).

Exposure to high altitudes

This presents another risk factor in pregnancy, particularly when combined with sports or other exercise activities because of the larger adaptive capacity to the relative hypoxaemia when the body is at rest than when exercising (Lenfant & Sullivan 1971). For a newcomer to altitudes above 2500 m there must be a rapid onset of the acclimatization processes if the symptoms caused by hypoxia are to be mitigated and the capacity for physical work and sport preserved. It is known that many of the most effective adaptive processes require several hours or even days to develop fully, so that pregnant women who want to be physically active should be advised to be extra careful, especially for the first days after acute exposure (Huch 1989). For one thing, during this time they could suffer from so-called acute mountain sickness with its symptoms of vomiting, respiratory dyspnoea and dizziness; 30% of all those exposed to altitudes no higher than 3000 m are affected by this illness (Johnson & Rock 1988). Another factor is the great stress engendered by the initial over-reactive increase in ventilation and cardiac output (Huch 1989), as this might negatively affect the uteroplacental circulation and the fetus. There are no direct blood gas or blood flow measurements on record of human fetuses exposed acutely to high altitude, but a tendency to suspicious fetal heart rate patterns was seen after simulated and actual exposure to moderate altitudes when combined with moderate physical stress (Baumann *et al* 1985). The disadvantage to the fetus of such conditions has been shown by Makowski *et al* (1968) in animal studies It took several days for the pregnant animal's oxygen content and saturation to normalize after exposure to high altitudes and in the umbilical vein the lowest saturation was measured between the second and fourth days, after exposure to altitude.

Hyperthermia

The most serious argument against sport during pregnancy concerns the intensity of the activity, since the consequences—maternal hyperthermia and a redistribution of the blood to the working muscles and in the skin for thermoregulation—can be injurious to the fetus. Hyperthermia is a natural result of certain types of sport; values of up to 41°C have been recorded for long-distance runs, depending on the duration and the ambient temperature (Metz 1983). Two pregnancy-specific changes must be mentioned. The woman's already less than advantageous ratio of surface area to body mass becomes even smaller in pregnancy due to the growing uterus, and the fetus is also an additional source of heat. Because of the considerable vasodilation in the skin during pregnancy (de Swiet 1980), one might also assume that the capacity for heat elimination during pregnancy is lowered. Two recent reports, however, suggest even the opposite. After a heat stress, both the skin and core temperatures decreased more rapidly in late pregnancy than in the non-pregnant state or in early pregnancy (Vähä-Eskeli & Erkkola 1989) Rectal temperature and peak core temperature reached during exercise also decrease more rapidly in the ensuing periods of rest as pregnancy progresses (Clapp 1989). Hence, these studies suggest that heat dissipation in pregnancy may even be enhanced. Hyperthermia has at least four disadvantageous effects: (i) teratogenic effects of core temperatures of ≥40°C in early pregnancy have been noted in animal studies (Editorial 1978; Kilham & Ferm 1976); (ii) the shift to the right of the maternal and fetal haemoglobin binding curves: though this results in an improved oxygen supply to the placenta, in fetal blood oxygen uptake becomes more difficult; (iii) the increased O_2 consumption; and (iv) an increase of the blood flow to the skin for thermoregulation.

Blood flow redistribution

It is well established that the increase in blood flow to the skin and to the working muscles is a result of a redistribution of cardiac output at the expense, *inter alia,* of the flow in the splanchnic area (Rowell 1974). Whether in women uterine blood flow during exercise is maintained at a level sufficient to satisfy the needs of the fetoplacental unit is largely unknown. In several studies on pregnant animals, it has been observed that uterine blood flow decreases by 20–60% during exercise (Chandler & Bell 1981; Clapp 1980; Longo *et al.* 1978; Lotgering *et al.* 1983). On the other hand, within 20 min after exercise, the flow returns to normal, sometimes with a slight overshoot (Lotgering *et al.* 1983) Furthermore, other changes might fully or partially compensate for the extent of blood flow reduction, such as flow redistribution within the uteroplacental unit favouring intervillous space flow at the expense of myometrial flow (Curet *et al.* 1976; Hohimer *et al.* 1984), increased O_2 extraction from the blood, and haemoconcentration at the beginning of exercise (Lotgering *et al.* 1983) with an increase in O_2 transport capacity.

There are very few human studies on this topic. Myometrial flow has been shown to decrease during exercise in the supine position (Morris *et al.* 1956). After moderate exercise the intervillous flow was comparable to pre-exercise levels in healthy women (Rauramo & Forss 1988*a*). Recent non-invasive Doppler ultrasound investigations in healthy pregnant women during light or moderate exercise have confirmed this (Baumann *et al.* 1989; Drack *et al.* 1988; Moore *et al.* 1988; Pijpers *et al.* 1984; Steegers *et al.* 1988). Resistance indices in the uteroplacental vessels did not change with exercise, but in women with pregnancy-induced hypertension or intrauterine growth retardation, exercise could impair uteroplacental blood flow (Campbell *et al.* 1983). Using radioactive xenon, significantly lowered myometrial blood flow after exercise was also observed by Rauramo & Forss (1988*b*) in hypertensive women.

Since it is often technically difficult to assess blood flow and changes *during* exercise, interpretation of measurements made *after* exercise requires caution. After exercise the uterine blood flow might very rapidly return to or above the pre-exercise level. It is conceivable that uterine circulation can also decrease during moderate or heavy aerobic exercise in women. Yet, as in animals, other compensatory mechanisms may guarantee that the fetal well-being is also maintained during exercise at most times. On the other hand, there are indirect reports which show that in some situations the safety limits of exercise may have been exceeded. Fetal bradycardia has been observed during strenuous exercise (Artal *et al.* 1984; Bung *et al.* 1989; Clapp 1985), and reductions in birthweight, dependent on the intensity of the physical activity during pregnancy, have been recorded (Clapp & Dickstein 1984). It must then be assumed that endurance during physical activity in pregnancy has certain limits. Even healthy women and, as seen in one of our own studies (Bung *et al.* 1989), women who were professional athletes before conception have no guarantee that sufficient uteroplacental blood flow will be maintained during intensive physical exertion. The limits of exertion a pregnant woman can safely endure are individual and are related to her physical condition. Since competitive and highly demanding sports require maximal motivation and a maximal adjustment of physical resources, in the absence of accurate and sensitive tolerance limits, participation in competitions and high-level performance training to the usual degree must be discouraged throughout pregnancy. This advice is especially important in the first trimester, when subjective limits usually are not yet noticeable.

Exercise and pregnancy

The fact that pregnant women can and do perform feats requiring a high level of physical fitness is often (incorrectly) used as proof of the physical capabilities of pregnant women and the compatibility of sport and pregnancy. It is true that records have been set and competitions won by women who are pregnant (Bruser 1968; Zaharieva 1972). Participation in the Olympics by pregnant women is often mentioned in the press, as is the seemingly normal course and outcome of pregnancy for athletes who continue their training during pregnancy. And pregnancy itself seems to be an ideal long-term endurance training, since many athletes are in top form after delivery (Brownlee 1988).

These individual observations suggest that the pregnancy-induced physiological alterations may not be necessarily disadvantageous for physical performance capacity. Theoretically, at least some of the alterations during pregnancy which are relevant for physical performance, such as increases in cardiac output, blood and plasma volumes in ventilation and oxygen transport capacity, are such as to even improve performance. It is also to be noted that pregnancy changes many of the variables in the same way as regular training. An editorial in the *Lancet* (Editorial 1985) discussed the surprising parallel between long-term training and pregnancy with respect to blood volume. In both cases there is a haemodilution as a result of an over-proportional increase in the plasma volume in comparison with the new production of erythrocytes. However, it is also easy to imagine that the changes which work positively on the performance capacity might be counter-balanced by pregnancy-related features such as weight increase, shifting of the body's centre of gravity, increased venous capacity, increase in oxygen consumption, decrease in buffer bases and, for instance, increased regulatory demand during orthostasis.

Objective measurements of physical work capacity (PWC) have so far not been able to give a clear answer to the question concerning a possible PWC increase due to pregnancy itself. The PWC is most reliably determined by measuring a person's maximal oxygen consumption, $\dot{V}o_2$ max. Submaximal tests can be performed either by measuring the oxygen consumption or heart rate at a given amount of work. Alternatively, the amount of work at a defined heart rate or oxygen consumption can be measured. Only a few investigations have been made under the most strenuous circumstances, that is exhaustive exercise, to determine $\dot{V}o_2$ max. (Artal *et al.* 1986; Dressendorfer 1978; Lotgering *et al.* 1988; South-Paul *et al.* 1988). South-Paul *et al.* (1988) compared changes in $\dot{V}o_2$ max. between an exercising and non-exercising group of pregnant women at 20 and 30 weeks. In both groups there was a slight increase in maximal oxygen consumption, more pronounced in the exercising group. Dressendorfer (1978) studied one highly trained woman. $\dot{V}o_2$ max. decreased during pregnancy, yet the amount of daily exercise also decreased. Artal (1986) compared $\dot{V}o_2$ max. (weight-bearing exercise) in a group of pregnant and non-pregnant women and found a decrease. Lotgering *et al.* (1988), in contrast, saw maximal oxygen consumption in a non-weight-bearing exercise unaffected by pregnancy. Hence it appears that results of investigations on the effect of pregnancy upon $\dot{V}o_2$ max. in previously highly trained women may also be influenced by changes in the intensity of training.

It is even more difficult to draw conclusions from submaximal tests. PWC at a given heart rate (e.g. 170 beats/min) or at a given oxygen consumption rate is not only affected by $\dot{V}o_2$ max. but also by a variety of other factors, including motivation (Lotgering *et al.* 1986). PWC_{170} has been found to remain unchanged during pregnancy (Dahlström & Ihrman 1960*a*, 1960*b*; Gemzell *et al.* 1957; Soiva *et al.* 1963), to decrease (Sandstrom 1974), or to be comparable with values in a non-pregnant sample (Dibblee & Graham 1983; Erkkola 1975). One could be tempted to summarize these inconsistent findings by postulating that physical work capacity is not significantly affected by pregnancy, and in no case particularly increased. Physical training during pregnancy, however, has been shown to increase the PWC (Erkkola 1976*a*).

Very few data are available on the postpartum recovery, quality of lactation and resumption of menstruation in mothers who start training within a short time span after labour. Zaharieva & Sigler (1963) studied 207 top athletes and found that 76% of the women had resumed training within 6 months of delivery; fewer than 10% did not breast-feed their babies and almost 40% reported good breast-feeding. More information is needed to be able to counsel women about the effects of strenuous training during the puerperium. The resumption of menstruation during training might also be related to the fact that oligo- and amenorrhea are two to four times more common in athletes than in the general population (Shangold 1985).

Conclusions and recommendations

Based on current information, some conclusions and practical advice can be presented Mild to moderate physical exercise is not harmful to the normal healthy pregnant woman or her fetus. If the woman is willing to start a gradually increasing exercise programme during pregnancy to improve her physical performance, this can be safely done, preferably, however, under medical supervision. When selecting the type of exercise, particular consideration must be given to the changes in weight, balance and ligaments so that the risk of athletic injuries is minimized. In the light of the effects of exercise upon the uterine circulation it may also be reasonable to recommend interval-type exercises and the avoidance of long continuous exercises. The basic principle is that a healthy pregnant woman is allowed to exercise as she pleases as long as the pregnancy is normal and she avoids exhaustion. Women with pregnancy disorders, such as threatened miscarriage or preterm labour, uterine haemorrhage, pre-eclampsia, fetal growth retardation, must be advised to refrain from exercise, possibly for the rest of the pregnancy.

When a top athlete becomes pregnant and wants to continue with training and possibly also to participate in competitions, problems may arise. Generally she has already trained hard and extensively before knowing about the pregnancy. If she is heading for a certain competitive event and if she cannot be persuaded to give up this idea, a good follow-up must be organized. During the first trimester it is best to monitor fetal growth by weekly or biweekly ultrasound scans. If the level of training remains high also during the second trimester, uterine artery blood flow velocity waveforms recorded from 18 weeks gestation at rest or even after exercise might also provide information on the safety of the training. For the rare occasions when a woman continues strenuous training during the third trimester, monitoring with cardiotocography at rest and after standardized treadmill or bicycle ergometer exercise may also be advisable. However, pregnancy with its potential complications and possible negative side-effects may militate against participation or top performance. Therefore, reliable contraceptive methods should be readily available for all female athletes as long as they want to train and compete at top levels.

Good physical condition is only one factor involved in the successful outcome of pregnancy. Modern perinatal care attempts to attain good results even where the physical condition of the pregnant woman is less than desired. The goal of maternal care and counselling is a healthy child, and the counselling concerning the physical activities and exercise during pregnancy should serve this goal. This counselling should not be of a compelling but of an encouraging and instructive nature for women who are not used to physical activities, and assenting for women who are used to regular exercise. Though the evidence of the beneficial effects of good physical condition upon the course of pregnancy and labour is still scarce, an awareness that one is in good physical condition generally is a psychological bonus helping the women to withstand the strains of pregnancy and motherhood.

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Erratum

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Uteroplacental Doppler flow velocity waveforms in the second trimester. A complex circulation

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In the Summary on page 1040, line two, the unselected group of women should read 977 and not 993 as stated. On page 1042, column two, line seven, should read· '. . . available for analysis, 34 proved to be under 16 . . .'

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Relaxin in sera during the luteal phase of in-vitro fertilization cycles

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Summary. To identify the time when relaxin can first be detected in peripheral sera after in-vitro fertilization (IVF) and embryo transfer, blood samples were collected from 20 women up to 14 days after oocyte retrieval. Sixteen women did not become pregnant and in eight of them relaxin (but not beta-human chorionic gonadotrophin, β-hCG) was measurable for the first time at days 6 to 12. Concentrations of other hormones measured were also different in these eight women compared with the remaining eight non-pregnant women; their serum concentrations of 17α-OH progesterone, progesterone and oestradiol were higher but concentrations of luteinizing hormone and follicle-stimulating hormone were lower. Three women became pregnant; relaxin and β-hCG were first detected on the same day (10 to 12). The remaining woman had increased β-hCG levels but did not develop a clinical pregnancy. Measurement of serum relaxin during IVF cycles may allow assessment of corpora luteal function before its identification by levels of steroid hormones.

The functions of relaxin in human pregnancy that have been described are concerned with events related to accommodation of the growing fetus and its safe birth at term (Bryant-Greenwood 1982; Sherwood 1988). However, relaxin can be measured in maternal circulation within weeks of fertilization and the levels are highest in the first trimester (Bell *et al.* 1987). It seems possible therefore that relaxin may also be involved in events of early gestation. If so, identification of its function may aid explanation and reversal of the high rate of failure of early pregnancies, especially in in-vitro fertilization and embryo transfer (IVF-ET) programmes.

This study was designed to determine the earliest date in pregnancy when immunoreactive relaxin could be measured in the peripheral circulation and to relate its concentration in the luteal phase of pregnancy to those of other hormones of reproduction.

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Subjects and methods

The 20 women recruited to this study were participating in the Monash University IVF-ET programme and all gave written consent before involvement in the study. All procedures used were approved by the human ethics committees of Monash University and the Howard Florey Institute. IVF cycles were stimulated by clomiphene citrate (Clomid, Merrill Dow, Sydney, Australia; 100 mg/day) and human menopausal gonadotrophin (hMG) (Pergonal, Serono, Rome, Italy; 150 iu/day) (Okamoto *et al.* 1986). Human chorionic gonadotrophin (hCG; 5000 iu) was administered to 17 women who did not have increased plasma luteinizing hormone (LH) concentrations near the day predicted for the LH peak. Laparoscopic oocyte retrieval was performed 21–28 h after hCG injection and embryos were transferred after a further 2 days.

Blood samples were collected on alternate days, 2 to 14 days after laparoscopy for radioimmunoassay (RIA) of hormones. Serum relaxin was measured using an RIA based on a synthetic analogue of human relaxin (Eddie *et al.* 1986, 1989). The between-assay coefficent of variation was 7·7% at 97·0 pg/ml (n=16). Within-assay coefficents of variation were 10·9% at 50 pg/ml, 6·7% at 100 pg/ml, and 4·8% at 180 pg/ml. Sensitivity (2 SD from 0) was 11·2, SD 1·3 pg/ml. Also measured in sera were the beta subunit of hCG (β-hCG; RIA-Quant, Malinckrodt, Inc., St Louis, MO, USA), follicle-stimulating hormone (FSH; Amerlex-M, Amersham International plc, Amersham, UK) using the second International Reference Preparation (IRP) FSH as standard, and LH (LH RIA, Diagnostic Products Corp., Los Angeles, CA, USA) using the second IRP LH as standard. Oestradiol and progesterone were measured using Coat-a-Count RIAs (Diagnostic Products Corp , Los Angeles, CA, USA). Details of all these assays have been published (Eddie *et al.* 1986, 1989; McLachlan *et al.* 1987). Serum 17α-OH progesterone was measured by RIA following extraction with ethyl acetate and using an antiserum from Steranti Research Ltd, UK, and tritiated tracer from Amersham International plc, UK. Cross-reactivities with progesterone, 11-deoxycortisol and 5α-pregnanedione were 2·2, 0·3 and 1·1% respectively. Between-assay coefficients of variation were 9·9% at 18·1 pg/ml, 9·4% at 68·0 pg/ml and 12·2% at 246 pg/ml (n=7). Within-assay coefficients of variation were 8·9% as 44·0 pg/ml, 7·7% at 137·8 pg/ml, and 9·1% at 171·0 pg/ml.

Differences in hormone concentrations between groups for each day were evaluated by analysis of variance following logarithmic transformation of the data.

Results

Of the 20 women in the study 16 did not become pregnant, but eight of them had measurable concentrations of relaxin (>11 pg/ml) in 1–4 serum samples (Fig. 1). Relaxin was first detected in four of these women in samples obtained on days 6 or 8, and this was earlier than in the women who were pregnant. No samples collected after day 6 from any of the 16 non-pregnant women had detectable levels of β-hCG (<1·7 miu/ml).

Three women became pregnant. Relaxin and β-hCG were first detected on days 10, 11 and 12 respectively in these three women. Relaxin concentrations were rising at day 14 (Fig. 2). One woman had β-hCG levels 2·4 and 10·4 miu/ml on days 12 and 14 respectively but no clinical signs of pregnancy appeared. Data from this woman were not included in the statistical analyses

In the eight non-pregnant women who had measurable levels of relaxin in at least one serum sample, levels of all the other hormones measured also differed from those in the other eight non-pregnant women. Levels of 17α-OH progesterone and progesterone were higher on days 8 and 10, and levels of oestradiol were higher on days 12 and 14 (Fig. 3). However, concentrations of LH and FSH were lower on days 12 and 14 (Fig. 4)

The mean number of follicles punctured at oocyte retrieval did not differ between the non-pregnant women who had or did not have measurable levels of relaxin (6·38, SD 2·72 and 4·50, SD 2·39 follicles) or the three pregnant women (6·00, SD 2·65 follicles).

Discussion

The corpus luteum is likely to be the site of synthesis of relaxin in early pregnancy. It is the only tissue in which the mRNA for human relaxin has been identified (Hudson *et al.* 1984). Inconsistent results have been obtained from studies using indirect methods involving extraction and immunohistochemistry to demonstrate relaxin in tissues other than the corpus luteum (Bryant-Greenwood 1982; Sherwood 1988).

The secretion of relaxin in some non-pregnant women during IVF cycles cannot be explained

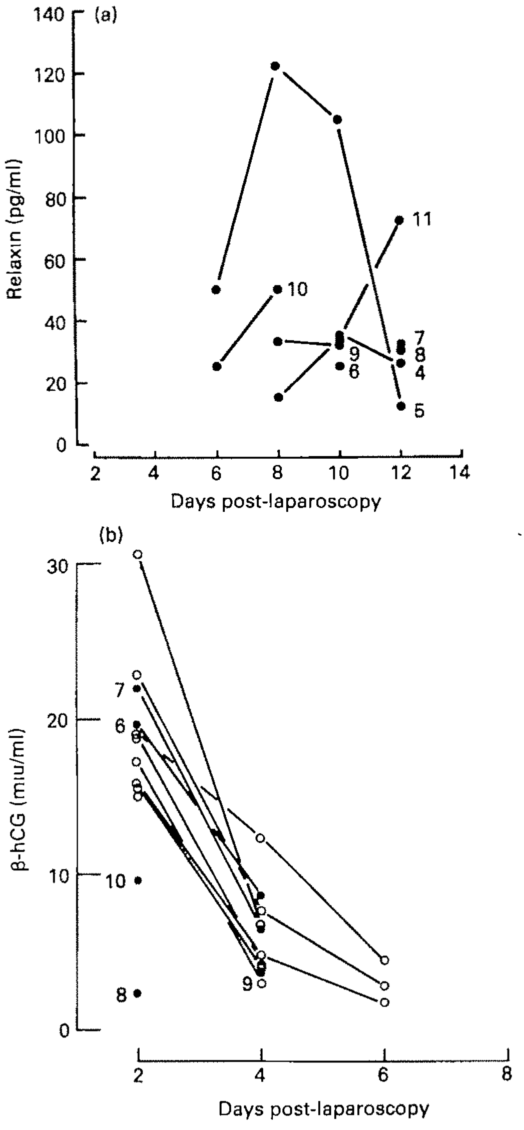

Fig. 1. Serum relaxin (a) and β-hCG (b) concentrations in 16 non-pregnant women at 2–14 days after laparoscopy for oocyte retrieval. The solid lines join data points from individual women who had detectable concentrations of relaxin (>11 pg/ml) and of β-hCG (>1·7 miu/ml). Women who had at least one serum sample with relaxin levels >11pg/ml are identified by numbers and their hormone concentrations are shown by closed circles (●). Open circles (○) show β-hCG levels in the other women without detectable relaxin levels in their serum samples.

by presuming that these women had a greater number of corpora lutea, as there were no differences in the number of follicles punctured at oocyte retrieval. The corpora lutea in these women may have developed further than in the others. Higher 17α-OH progesterone levels also indicate greater luteal function. However, this difference in luteal function would have been difficult to identify by measurement of steroid hormones alone and did not occur until some days after the appearance of relaxin in the sera. Measurement of serum relaxin during IVF cycles may have diagnostic value in the early assessment of luteal function.

The appearance of relaxin in the serum of non-pregnant women days before that in pregnant women may be significant. Because the maintenance of early pregnancy requires synchrony of factors from the embryo, endometrium and corpus luteum, early secretion of relaxin could indicate asynchronous luteal function that results in loss of the embryo. Relaxin

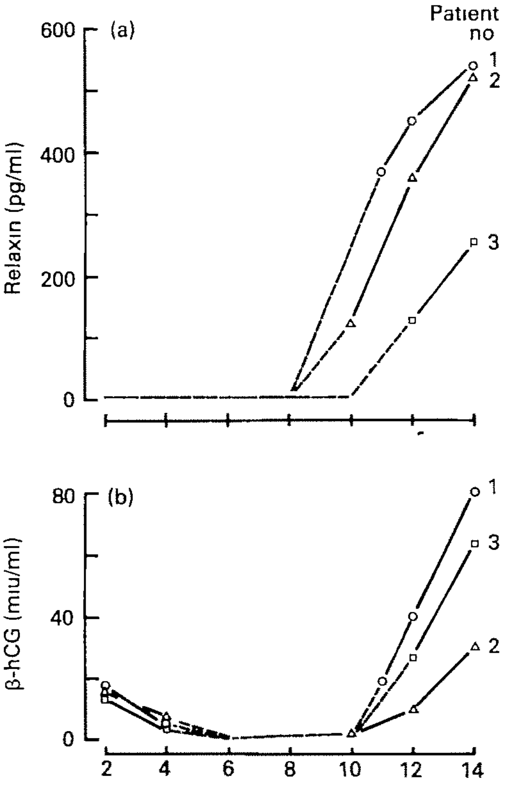

Fig. 2. Relaxin (a) and β-hCG (b) concentrations in sera collected from the three pregnant women on days following laparoscopy for oocyte retrieval. Broken lines indicate that hormone concentrations in one of two consecutive samples were less than the sensitivity of the RIA (relaxin 11 pg/ml, β-hCG 1·7 miu/ml).

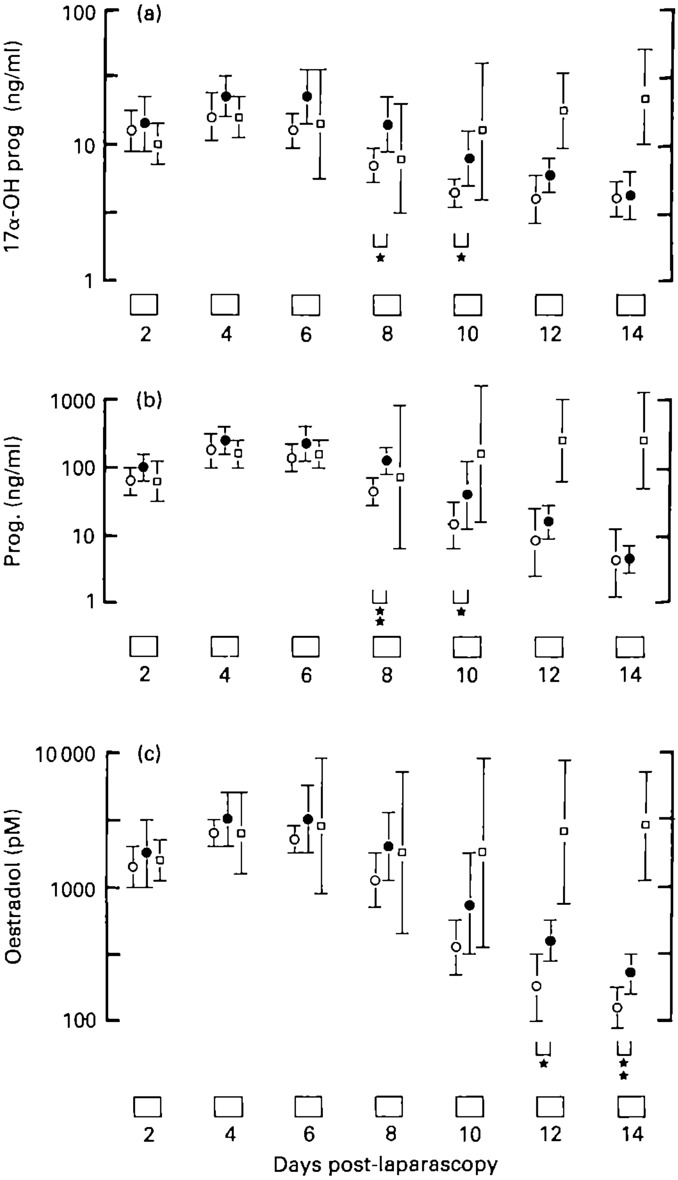

Fig. 3. 17α-OH progesterone (a), progesterone (b) and oestradiol (c) concentrations in sera collected at 2–14 days after laparoscopic oocyte retrieval from three pregnant women (☐) and 16 non-pregnant women grouped into those having at least one sample with measurable levels of relaxin (●, $n=8$) and those without measurable relaxin levels (○, $n=8$) Results are expressed as geometric means and 95% confidence intervals. *$P<0{\cdot}05$, **$P<0{\cdot}01$ comparing hormone concentrations in samples taken from the non-pregnant women on the same day.

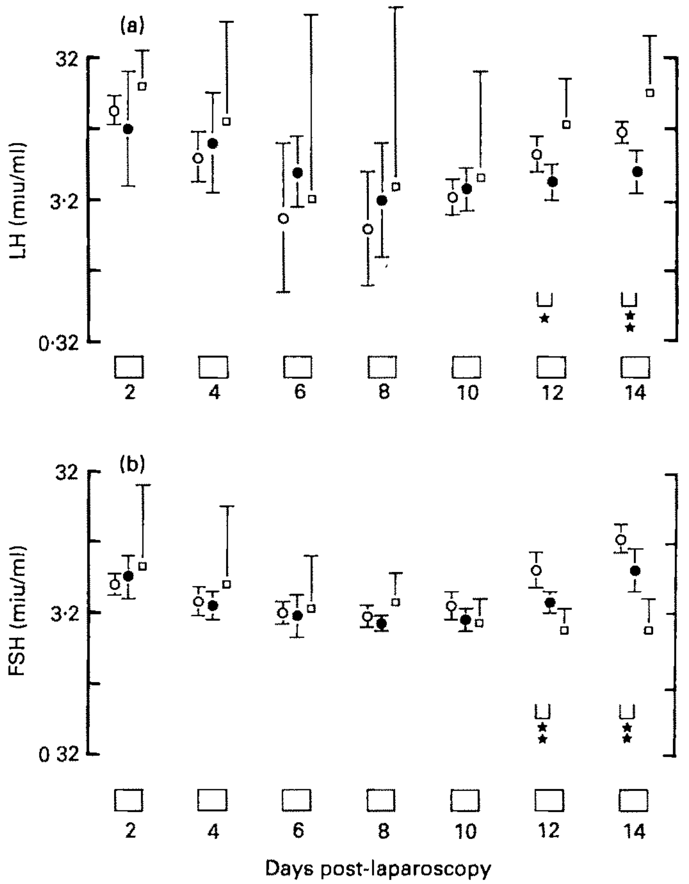

Fig. 4. LH (a) and FSH (b) concentrations in sera from the pregnant women (□) and non-pregnant women (○, ●) on the days following laparoscopy for oocyte retrieval Details given in the legend for Fig 3.

may aid the survival of the embryo by influencing events involved in nidation, such as the inhibition of uterine movement. It is possible that treatment with exogenous relaxin in women with poor or absent luteal function could contribute to the success of their IVF-ET cycles.

In the pregnant women, relaxin was first detected in the serum samples obtained at 10–12 days after fertilization of the ova *in vitro,* the same day on which β-hCG was first detected. This is similar to the findings reported by Quagliarello *et al.* (1979) who detected relaxin, using an RIA for porcine relaxin, in peripheral sera from a woman ten days after conception. Levels of other hormones were not reported.

There is some evidence that hCG stimulates the secretion of relaxin *in vivo* (Quagliarello *et al.* 1980; Thomas *et al.* 1980). Our data are consistent with that hypothesis, as the day of first detection and the rate of increase in concentrations of both relaxin and β-hCG in pregnancy sera are similar. The finding of measurable amounts of relaxin in the sera of eight of the non-pregnant women in the absence of detectable β-hCG may indicate that very low concentrations of hCG are capable of stimulating relaxin secretion, or that this function is served by pituitary LH. Alternatively, other, as yet unidentified stimuli may exist.

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Osteopenia in pregnancy during long-term heparin treatment: A radiological study post partum

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Summary. Osteopenia, sometimes with compression fractures of the spine, is a side-effect of long-term heparin treatment. The frequency is unknown. In this study, 70 women were given subcutaneous heparin as therapy for, or prophylaxis against, thromboembolism during pregnancy. All, except two, were examined by X-ray of the spine and hip first week post partum. The duration of treatment and the dosage of heparin varied. There were 12 (17%) with obvious osteopenia, including two women with multiple fractures of the spine (3%). Re-examination 6–12 months post partum showed that the changes were reversible in most cases. Another 18 women were examined about three years after heparin treatment during pregnancy. No obvious osteopenia was found among them or in a control group of 30 women examined in the first week post partum. The degree of osteopenia was not correlated with either the heparin dose or the duration of treatment. Women treated with heparin in consecutive pregnancies do not seem to have an increased risk of osteopenia.

Thromoembolic complications during pregnancy and puerperium constitute one of the main causes of maternal mortality today (Department of Health and Social Security, London 1986; Bonnar 1987). Previous deep thrombosis is associated with a risk of further thrombosis during pregnancy of at least 10% (Badaracco & Vessey 1974; Tengborn *et al.* 1989). These women are frequently given heparin prophylactically during pregnancy (Spearing *et al.* 1978; de Swiet *et al.* 1980; Hellgren & Nygårds 1982; Bonnar 1987). After an acute deep thrombosis, an initially high dose of heparin is often followed by a prophylactic lower dose for the remainder of the pregnancy (Hellgren & Nygårds 1982, Letsky & de Swiet 1984).

Oral anticoagulants such as warfarin are not generally recommended during pregnancy because they cross the placenta. This may result in defective fetal development (chondrodysplasia punctata), mental retardation, and blindness, and there may be fetal or maternal bleeding (Hall *et al.* 1980; Stevenson *et al.* 1980). Long-term heparin treatment, on the other hand, may cause osteoporosis in the mother, sometimes with multiple spinal fractures (Squires & Pinch 1979; Aarskog *et al.* 1980; Wise & Hall 1980; Megard *et al.* 1982; Griffiths & Liu 1984; Zimran *et al.* 1986). Heparin does not pass

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the placenta in amounts sufficient to influence the fetus (Flessa *et al.* 1965).

The frequency and pathogenesis of heparin-induced osteoporosis is not fully understood. The purpose of this study was to assess the incidence of heparin-induced osteopenia and to determine whether the risk was correlated with the amount of heparin and duration of treatment. Furthermore we wanted to investigate if the osteopenia was reversible.

Patients and methods

From July 1980 to March 1984, all patients who received long-term heparin treatment therapeutically or prophylactically during pregnancy had X-ray examination of the spine and hip in the first week post partum, except for two who were examined after 8 and 5 weeks, respectively. In all, 70 patients and 30 controls were studied.

All the women agreed to take part in the research which had been approved by the local ethics committee of the Karolinska Hospital.

Treatment group

This group included 25 pregnant women with confirmed deep thrombosis. Heparin treatment was started as soon as the diagnosis was made (mean 20th week; range 7–38 weeks gestation). During the first week of treatment all the patients received a continuous intravenous heparin infusion that maintained an activated partial thromboplastin time (APTT) of 70–100 s (reference value 25–35 s). Thereafter, the heparin was given subcutaneously twice daily. The dose was adjusted to provide a 10–15 s prolongation of the upper reference value of the APTT before the morning dose so that the values were 45–50 s during the first month. For the remainder of the pregnancy the dosage was adjusted to an APTT of 45–50 s at the peak level about 3 h after injection, our prophylactic high-dose regimen (see below). The average heparin dose was 31 400 IU/24 h and the mean duration of treatment was 16·6 weeks (Table 1). Labour was usually induced and, during labour, the women were given either heparin 5000 IU subcutaneously every 8 h, or 500 ml dextran 70 intravenously twice in 24 h. Post partum they were either transferred to oral anticoagulants or continued with subcutaneous heparin 10 000–15 000 IU/24 h for at least 6 weeks.

Prophylaxis group

The 45 pregnant women included in this group had all had a history of verified thromboembolism with two exceptions (see below). Twelve had received heparin during at least one previous pregnancy and seven were investigated by X-ray of the spine and hip on both occasions.

All the women were healthy except for their history of thromboembolism. Heparin prophylaxis was usually started early in pregnancy (mean 13th week, range 6–38 weeks). Twelve of these 45 women had had their thrombosis during pregnancy and six in the puerperium (three after caesarean section). Two of the thromboembolic episodes followed surgery in the non-pregnant state and 16 were associated with oral contraception containing oestrogens. Five of the women had had idiopathic thromboembolism and two were associated with coagulopathy (defective fibrinolysis and F XIII deficiency). Two women were given heparin prophylactically without any history of thrombosis, one because of congenital antithrombin III deficiency and the other because she had a mechanical heart valve prosthesis. The latter was using oral anticoagulants at conception and transferred to heparin in the 8th week of pregnancy.

Two prophylactic dose regimens were used. One was a high-dose regimen which was given to 24 women. They received heparin subcutanously twice daily and the dose was adjusted to maintain their APTT at 45–50 s about 3 h after injection. These 24 women received an average dose of 24 600 IU/24 h and the mean duration of treatment was 24·8 weeks (range 2–33 weeks) (Table 1). The second was a low-dose regimen and was used in the other 21 women. Heparin was given subcutaneously twice daily and the dose was adjusted according to the plasma heparin concentration measured as anti-FXa activity with a chromogenic peptide substrate (S-22 22 Kabi AB, Stockholm, Sweden) (Teien & Lie 1977). A level of around 0·1 IU/ml 3 h after injection was considered satisfactory (Bonnar 1987). This 'low-dose' group had an average need of heparin of 17 500 IU/24 h and the mean duration of treatment was 24·7 weeks (range 6–32 weeks) (Table 1).

During delivery, all the women receiving prophylaxis were given either heparin subcuta-

Table 1. Obstetric data and heparin dosage and duration of treatment in patients and controls. Mean values

	Treatment group	Prophylaxis group		Previously treated		Control group
		High-dose	Low-dose	Treatment	Prophylaxis	
Number of patients	25	24	21	10	8	30
Age at X-ray (years)	28·5	30·7	28·5	30·0	29·3	27·8
Pregnancy weight (kg)	60·8	61·7	62·7	58 3	60·4	58·3
Smokers (%)	28	42	43	44	28	30
Primipara (%)	64	46	43	50	50	57
Gestation (weeks)	38·8	38·0	37·8	37·5	38·0	38·4
Heparin therapy						
Mean dosage (IU × 10^3/24 h)	31·4	26·4	17·5	35·3	30·3	—
Duration (weeks)	16·6	24·8	24·7	16·0	28·3	—
Total amount (IU × 10^6)	3·7	4·6	3·0	4·0	5·9	—

neously or dextran 70 in the same manner as those in the treatment group. After delivery they were given heparin, 10 000–15 000 IU/24 h, for 6 weeks post partum except for the woman with the artificial heart valve who recommenced taking oral anticoagulants.

Control group

The 30 pregnant women recruited to this group were all healthy and not receiving medication. They were similar to the other two groups with regard to age, weight, smoking, parity and gestational age (Table 1). Their pregnancies were all normal.

Previously-treated groups

This group consisted of 18 women who had undergone heparin treatment during pregnancy (10 therapeutically and eight high-dose prophylactically) 1–4 years earlier (mean 2·7 years) without subsequent spinal X-ray examination. They were called for X-ray examination in order to investigate if there were still signs of osteopenia. Heparin was given in the form of unfractionated standard sodium heparin prepared from pig intestinal mucosa (Kabi AB, Stockholm, Sweden). When given subcutaneously, the women injected themselves in the thigh or hip every 12 h.

Radiological examination

All the pregnant women in this study were examined the first week post partum except for two women in the treatment group who were examined 8 and 5 weeks post partum while still on heparin. The women treated previously were examined 1–4 years after delivery. Films were taken of the thoraco-lumbar spine in anterior–posterior (A–P) and lateral projections and of the right hip in A–P view. The examinations were performed with the same standard X-ray equipment, the same film type and intensifying screens, as well as by the same development equipment and by the same X-ray assistant. The films were assessed by only one radiologist who had more than 20 years' experience in this field The treated and the control women were mixed so that neither the assistant nor the radiologist knew their history or treatment. The grading of osteopenia of the spine was subjective, and was based on a comparison of the density of the cortex and the spongiosa. The degree of osteopenia was graded as follows: no osteopenia (0), suspected osteopenia (I), and obvious osteopenia (II). It was planned that the women with osteopenia should be examined again 6 months later and the results compared with the first examinations. However, only 13 of the 22 osteopenic women participated in the follow-up study. All films were reassessed blindly after about 1 year.

Statistical methods

Either the χ^2-test or Fisher's test were used to compare normally distributed variables. The Kruskal–Wallis non-parametric one-way analysis of variance was used when the distribution was not normal. A P value of $<0{\cdot}05$ was considered statistically significant.

Results

Of the 70 women treated with heparin 12 (17%)

had obvious osteopenia when they were examined post partum. No woman in the control group had obvious osteopenia ($P<0{\cdot}01$; Table 2). Furthermore, two women who received the high-dose prophylactic regimen had severe back pain post partum and X-ray examination showed osteopenia and multiple fractures of the spine in both of them. One woman had multiple compression fractures in the dorsal and lumbal vertebrae and decreased in height from 165 to 157 cm. Her back pain slowly improved during the next 2 years. The second woman developed backache in late pregnancy which became suddenly worse 9 weeks after delivery. At that time the vertebrae showed marked osteopenia but no fractures. Multiple fractures were shown at X-ray 6 months post partum. Her height decreased from 157 to 150 cm 2 years before her backache ceased. The other 10 women with obvious osteopenia had no symptoms and no fractures were detected either clinically or radiologically.

Osteopenia was suspected radiologically in 10 of the 70 women receiving heparin compared with 3 of the 30 in the control group (Table 2).

The prevalence of obvious osteopenia was similar in the three groups of women receiving heparin (treatment group and high and low-dose prophylaxis groups) (Table 2) Of the 45 women in the prophylaxis group, 12 had been treated with heparin previously during pregnancy. Seven women had had X-ray examination after the previous pregnancy as well, and in one of them the degree of osteopenia was more pronounced after the second pregnancy (Table 3).

For the study pregnancies, the grade of osteopenia is shown in relation to duration of heparin treatment (Fig. 1) and mean heparin dosage (Fig. 2). Table 4 shows the grade of osteopenia in relation to total amount of heparin, patient age, weight, parity and smoking. No statistically significant differences were seen.

Of the 22 heparin-treated women who were considered to have suspected or obvious osteopenia post partum, 13 were examined again by X-ray 6–24 months later (Table 5). In 11 of these 13 women the osteopenia was less marked and in nine of them the improvement was present 6–12 months after the end of the heparin treatment. Thus, in almost 70% of the women examined, the osteopenia had regressed within 12 months. In the two women with spinal fractures no change was seen after 6 months, but 2 years post partum both showed less osteopenia and were almost free from symptoms.

The women who had been treated previously with a high-dose heparin regimen were examined 1–4 years after delivery. In one there was suspected osteopenia but none had obvious osteopenia (Table 2).

Thrombosis did not recur in any of them.

Discussion

Heparin-induced osteoporosis was first described by Griffith *et al.* (1965) in a series of 117 patients treated with heparin for at least 8 months. In 107 of them treated for 1–15 years, the dosage had not exceeded 10 000 IU/day and none of them had any symptoms of compression fractures of the spine and were not examined radiologically. The other 10 patients (age range 49–69 years) had received 15 000–20 000 IU/day for 8–60 months; all were examined radiologically and six had osteopenia and fractures of the spine or rib. The other four had normal X-ray

Table 2. Spinal osteopenia after heparin treatment (A), prophylactic high (B_1) and low (B_2) dose regimen and controls (C) on X-ray first week* and 1–4 years post partum (D).

		Grade of osteopenia			
Time of X-ray	Group	Obvious (II)	Suspected (I)	Normal (0)	Total
First week post partum	A	5*	1	19	25
	B_1	4 (2)	6	14	24
	B_2	3	3	15	21
Total		12 (2)	10	48	70
Controls	C	0	3	27	30
1–4 years post partum	D	0	1	17	18

* In two women X-ray was performed in the 8th and 5th week, respectively.

Results are given as numbers of women (number in parenthesis denote those with spinal fractures).

Table 3. Seven women treated with heparin during consecutive pregnancies who had X-ray examinations post partum Prophylactically (P), therapeutically (T).

				Heparin		
Patient no	Pregnancy	Age (years)	Prepregnancy weight (kg)	Duration Pregn/puerp (weeks)	Mean dosage (IU × 10^3/24 h)	Osteopenia grade on X-ray
1	1	29	61	24/ 6	30 P	0
	2	32	59	32/ 6	13 P	0
2	1	31	64	24/ 6	35 P	0
	2	34	70	32/ 1	30 P	0
3	1	30	55	7/12	30 T	—
	2	33	56	29/ 8	18 P	II
	3	35	58	30/ 6	15 P	II
4	1	35		3/ 3	30 T	0
	2	36	60	30/ 3	15 P	II
5	1	23		15/ 8	30 T	II
	2	25	60	29/ 6	15 P	I
6	1	23		10/13	50 T	0
	2	24	70	22/ 6	23 P	0
7	1	28		6/13	45 T	0
	2	30	66	31/ 6	15 P	0

and three of them had received anabolic steroids prophylactically. There was no control group.

Since 1979, 11 case reports of heparin-induced osteopenia with spinal fractures have been published, six in connection with pregnancy (Squires & Pinch 1979; Aarskog *et al.* 1980; Wise & Hall 1980; Megard *et al.* 1982; Griffiths & Liu 1984; Zimran *et al.* 1986). The shortest duration of treatment was 12 weeks (Aarskog *et al.* 1980) and the lowest dose of heparin 10 000 IU/day (Griffiths & Liu 1984). Experimental osteoporosis with heparin treatment in rats has been reported after 500 IU heparin/kg b.w. for three months (Ambrus *et al.* 1978) and after 2000 IU heparin/kg b.w. for 33 days (Mätzsch *et al.* 1986).

In our study, conventional X-ray examination was used for grading the osteopenia as more sensitive methods such as photon absorptiometry were not available. When osteopenia is evident on ordinary X-ray films, a reduction of 30–50%

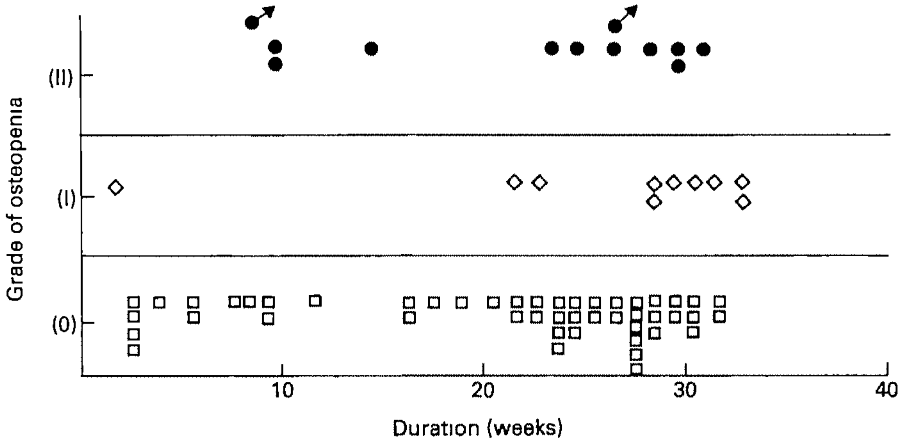

Fig. 1. Grade of osteopenia, of the spine on X-ray post partum in relation to duration of heparin treatment, (0) normal; (I) suspect; (II) obvious; ●↗ = fractures.

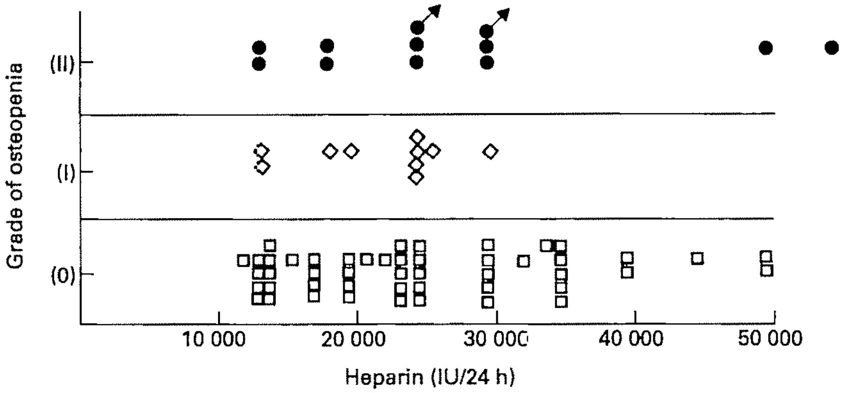

Fig. 2. Grade of osteopenia, of the spine on X-ray post partum in relation to mean dosage of heparin treatment (0) normal, (I) suspect; (II) obvious; ●↗ = fractures.

of bone mineral has occurred (Leroux 1973). Thus, our study may underestimate the occurrence of osteoporosis.

It is difficult to assess osteopenia from X-ray films. The most obvious evidence is compression fractures of the vertebrae. The judgment of osteopenia in the absence of fractures is subjective but this method gave consistent results in the present study. The films were examined without knowing whether they belonged to the treated or the control groups. None of the controls was classified as having obvious osteopenia. Furthermore, a second examination of the films about a year later gave almost identical results. This second examination was performed without the radiologist knowing the results of the original examination.

The results of our study indicate that long-term heparin treatment is associated with a considerable risk of osteopenia, 17% of the patients had obvious osteopenia and two women had symptoms and signs of compression fractures of the thoracic and lumbar spine. Both had been given high-dose thromboprophylaxis with heparin 25 000 IU/24 h for 27 weeks in one and 30 000 IU/24 h for 9 weeks in the other. The other 10 women with osteopenia had no back pain and no compression fractures of the spine on X-ray.

In our study the grade of osteopenia did not correlate with either the dose or the duration of heparin treatment. Not even a second pregnancy with heparin treatment influenced the degree of osteopenia. Our findings contrast with those of de Swiet *et al.* (1983) who noted that the phalangeal cortical area total area ratio was significantly less after long-term heparin therapy (>25 weeks) than after short-term therapy (<7 weeks). The demineralization was most marked in three women who had received heparin in a previous pregnancy.

X-ray examination 6 to 12 months post partum showed that the osteopenia is usually reversible. Of 13 women examined again 9 (70%) showed an improvement on X-ray. However, in the two patients with spinal fractures, no improvement was seen until 24 months post partum. Further evidence that bone calcification improves after the end of treatment is provided by our finding that of 18 women treated with long-term high-dose heparin in pregnancy on average 30 months earlier, only one had suspected osteopenia and none had obvious osteopenia. These findings are in contrast to those of de Swiet *et al.* (1983) who examined 20 heparin-treated women 1–28 months after delivery and still found signs of demineralization in metacarpal and phalangeal cortical areas 24 months after treatment had ceased.

The pathogenesis of heparin-induced bone loss is not fully understood. In an extensive review by Avioli (1975) different possible theories were discussed. One patient had low levels of 1,25-dihydroxy-vitamin-D (Aarskog *et al.* 1980) but this has not been found in others. Some experimental data suggest that heparin has a direct effect on the osteoblasts (Ellis & Peart 1970). In a study to be published by our group, ionized calcium was not reduced and there was no hyperparathyroidism in heparin-treated subjects. This suggests that the bone loss associated with heparin treatment in pregnancy is not a protection against hypocalcaemia or compensation for changed parathyroid function.

Our findings indicate that some women might

Table 4. Grade of osteopenia of the spine on X-ray post partum in relation to age, weight, parity, smoking, duration of heparin treatment and mean dosage of heparin. Mean (SD)

						Heparin treatment			
							Study pregnancy		
Grade of osteopenia	Number of patients	Age (years)	Pre-pregnancy weight (kg)	Primipara *n* (%)	Smokers *n* (%)	Total duration (weeks)	Duration (weeks)	Dosage (IU × 10^3/24 h)	Total amount (IU × 10^6)
Obvious (II)	12	28·3 (6·1)	62·3 (8·8)	5 (41·7)	4 (33·3)	27·6 (19·6)	22·3 (8·8)	28·0 (12·8)	4·1 (2·3)
Suspected (I)	10	28·7 (4·0)	63·5 (6·7)	4 (40·0)	3 (30·0)	35·7 (17·4)	26·4 (9·4)	22·4 (5·1)	4·1 (1·8)
Normal (0)	48	29·6 (6·5)	62·1 (9·8)	27 (56·3)	19 (39·6)	24·0 (13·9)	21·0 (9·4)	25·5 (9·6)	3·6 (1·9)

Table 5. Changes on X-ray of the spine 6–24 months post partum after heparin treatment for therapy (T) or as prophylaxis (P) in 13 patients with osteopenia

				Heparin treatment						
					Study pregnancy		Grade of osteopenia month post partum			
Parity	P/T	Age (years)	Pre-pregnancy weight (kg)	Total duration (weeks)	Duration (weeks)	Mean dosage (IU × 10^3/24 h)	1	6	12	24
2	P	32	64	36	27	25	II*	II	II	I
2	P	26	48	9	9	30	II*	II	II	I
2	P	33	59	26	26	30	II	II	I	
1	T	16	80	5	5	50	II			II
1	T	20	60	32	32	25	II		I	
1	T	23	67	15	15	30	II		I	
2	P	36	60	36	30	15	II	0		
1	P	31	64	29	29	25	I	I		
2	P	33	70	44	31	30	I		0	
2	P	24	54	34	33	15	I	0		
2	P	30	55	60	32	26	I	0		
1	P	23	61	24	23	25	I	0		
2	P	31	60	55	30	15	I	0		
Mean		27·5	61·7	31·2	24·7	26·2				
SD		6·0	7·9	16·2	9·3	9·2				

* Spinal fractures.

experience heparin-induced osteopenia throughout the dose range (15 000–55 000 IU/day) or duration range (9–32 weeks) (Figs. 1 and 2). Perhaps they are not capable of protecting themselves from bone resorption by increasing their levels of calcitonin, which is generally seen during heparin treatment in pregnancy (unpublished observations).

For the sake of safety, the amount of heparin during thromboprophylaxis should be kept as low as possible but without risking a thrombosis. As the individual need for heparin varies considerably, the anticoagulant effect should be measured (Letsky & de Swiet 1984; Bonnar 1987; Dahlman *et al.* 1989). When monitoring the effect by the relatively insensitive APTT, the dosage will on average be considerably higher than when monitoring the anticoagulant effect as anti-FXa activity (Dahlman *et al.* 1989) (see also Table 1).

The indication for long-term heparin treatment in pregnancy still remains. With regard to prophylactic treatment during pregnancy we today consider a history of previously verified thromboembolism as an indication for heparin treatment due to the high risk of recurrence of thrombosis with risk of fatal pulmonary embolism (Badaracco & Vessey 1974; Howell *et al.* 1983; Tengborn *et al.* 1989).

In the future, however, it may be possible to select certain women who can be given thromboprophylaxis with compression stockings alone and without heparin.

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Lack of correlation between a high caesarean section rate and improved prognosis for low-birthweight twins (<2500 g)

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Summary. The impact of birth by caesarean section on perinatal mortality was estimated for 9368 low-birthweight twins (<2500 g) born in Sweden between 1973 and 1985, by using national data from the Medical Birth Registry, National Board of Health and Welfare, Stockholm. During this period the caesarean section rate increased from 7–10% to 45–50% while concomitantly a sharp decrease in the perinatal mortality rate occurred. A causal relation between the increased rate of abdominal delivery and the improved prognosis for low birthweight twins might be expected. However, analysis of the results failed to show any correlation between these two variables. Factors other than route of delivery seem to have a greater impact on fetal outcome.

The perinatal mortality (PNM) rate for twins is 4–6 times as high as for singletons (Hoffman & Bakketeig 1984). The main obstetric cause of this is the increased frequency of preterm deliveries in twin pregnancies (Chervenak *et al.* 1984, Ho & Wu 1975). Great efforts to reduce this problem, including routine hospital care and tocolytic therapy, have had little impact on the PNM rate (Saunders *et al.* 1985; Rydhström *et al.* 1987)

In labour, particularly in the preterm period, twins are exposed to an increased risk of placental abruption, cord prolapse, dystocia, hypoxia and problems related to malpresentation. These factors are all associated with an increased rate of PNM. There has been an increasing trend in recent years to deliver twins at risk abdominally in order to reduce these complications. Thus, caesarean section (CS) has been advocated for non-vertex presentations (Cetrulo *et al.* 1980), for preterm breech presentations (Westgren & Paul 1985), and for twins weighing <1500 g (Barrett *et al.* 1982). Concern for the second twin has led some obstetricians to suggest abdominal delivery for all twin pregnancies (Ware 1971). However, no conclusive evidence of an improved fetal prognosis related to an increased CS rate has yet been presented.

Furthermore, assessment of the results has often been hampered by a relatively small number of births in each investigation. A few have been population-based studies (McCarthy *et al.* 1981; Medearis *et al.* 1979), or multicentre studies involving a large number of women (Grandjean & Papiernik 1983).

Since 1973, data from all deliveries in Sweden have been registered with the national Medical Birth Registry (MBR). The frequency of drop-outs (*vide infra*) has been low. This gave us the

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opportunity to collect a large population of twin pregnancies for a study on a nationwide basis and to perform an analysis of the impact of caesarean birth on PNM for low-birthweight twins (<2500 g).

Subjects and methods

The present study population comprised 9368 low-birthweight (<2500 g) twins (one or both twins of the pair), born in Sweden between 1973 and 1985. Data on gestational age, hour and mode of delivery, birthweight, and PNM were obtained from the MBR, National Board of Health and Welfare, Stockholm. The MBR stores records of all infants born at a gestational age of ≥28 completed weeks, or less if the fetuses are liveborn. PNM implies stillborn fetuses, or newborns dying within 7 days. According to official statistics, a total of 23 018 twins were born during the study period (Population Changes, 1974–86). Of these, 644 newborns were not on record at the MBR, giving a drop-out rate of 2·8%. The birthweight was missing for 0·5% of all twins.

The correlation (Spearman's rank correlation coefficient) between the CS rate and PNM was calculated during three different periods for each of the 24 counties in Sweden (Siegel 1956). However, a considerable variation in PNM was found due to the small number of twins born in each county. To overcome this problem, the correlation between the changes in the CS rate and PNM was calculated in the following way. For each county, two regression coefficients were determined: one describing CS rate with time (three periods: 1973–76, 1977–81, 1982–85), the other PNM with time. Regression coefficients were estimated using the technique described by Maxwell (1961). Finally, a correlation coefficient was determined using the two sets (CS, PNM) of regression coefficients as variates. If there is a causal relation between a high CS rate and a low PNM, a negative correlation coefficient is anticipated

An analysis of CS by time of day revealed a sharp increase in the CS rate between 08.00 and 13.00 hours. The hypothesis was tested that this high CS rate was associated with a low PNM rate. According to this the PNM rate for the infants born during these hours should be lower than the rate for infants born at other times during the day. Time of birth was missing for 0·4% of all twins.

The PNM ratio of second twin to first twin has been used as an index for a possible improvement in the prognosis for the second twin with a rising CS rate. A ratio of 1·0 indicates an identical PNM for the first and the second twin. To test whether changes in this ratio during the study period were significant, the Armitage–Cochran test with one degree of freedom (d.f.) was used (Armitage 1971). A P value <0·05 was considered significant.

Results

The CS rate for twins weighing <2500 g increased from 7·1% in 1973 to 47·4% in 1985 (Table 1). During the same period the PNM decreased from 17·9% to 5·9%.

The CS rates for the 24 counties varied between 2–28% in the first period (1973–76) and 17–77% in the last period (1982–85). The number of twin births in each county was about 130 (range 14–627) and the number of perinatally dead twins about 11 (range 0–86). No linear association between different CS rates and the PNM rates in the 24 counties could be found during any of the three periods 1973–76, 1977–81 and 1982–85 (Fig. 1). The correlation coefficient during the first period was −0·02 (t = 0·1 at 22 d.f., P>0·05), during the second −0·29 (t = −1·4 at 22 d.f., P>0·05) and during the third period 0·17 (t = 0·8 at 22 d.f., P>0·05).

A positive correlation coefficient of 0·11 was found when the change in CS rate between the three periods was plotted against the change in PNM for each county using estimated regression coefficients (Fig. 2). The correlation coefficient did not differ signficantly from 0·0 (t = 0·54 at 22 d.f., P>0·05).

The PNM rate was compared with the CS rate during each hour of the day (Fig. 3). The CS rate rose almost threefold between 08.00 and 13.00 hours, whereas the overall PNM varied little (8·2% to 11·3%). The highest rate of PNM was seen for twins born abdominally between 02.00 and 04.00 hours. Twins born by CS had a lower PNM than twins born vaginally between 07.00 and 13.00 hours and between 17.00 and 01.00 hours

The PNM of the second twin divided by that of the first twin was above unity during the first 11 years of the period (Fig. 4). A possible trend in the proportion of the second twin among all perinatally dead twins between 1973 and 1985 was tested using the Armitage–Cochran test; the

Table 1. Number of twins, perinatal mortality (PNM) and the caesarean section (CS) rate for low-birthweight twins (<2500 g)

	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985
n	798	842	780	704	655	688	725	711	701	636	666	686	776
CS (%)	7·1	9·3	11·9	20·5	27·5	30·8	35·4	44·6	49·6	46·4	48·3	50·7	47·4
PNM (%)	17·9	13·1	9·4	11·1	10·7	9·9	9·1	8·3	7·3	3·3	2·3	4·4	5·9

trend was not statistically significant (χ^2 = 1·2 at 1 d.f., P>0·05). The greatest variation in this ratio was found in the years 1981 and 1982 when the CS rate was stable between 45 and 51%.

Discussion

Concomitantly with a rising CS rate the PNM decreased for low birthweight twins born in Sweden between 1973 and 1985. However, the results of this study indicate that the reduced PNM is not related to an increased CS rate. Other population-based studies have suggested little impact on PNM of a rising CS rate (McCarthy *et al.* 1981; Medearis *et al.* 1979).

On the other hand, hospital-based studies, often from tertiary centres or from multicentre studies, give contradictory results. It has been suggested that CS is the optimal mode of delivery for twins with a birthweight <1500 g (Barrett *et al.* 1982). In a multicentre study, Grandjean & Papiernik (1983) found an increased PNM for twins born vaginally, yet no relation between the PNM and the different CS rates in the participating hospitals.

To avoid the obvious misleading simple correlation between the rising CS rate and the decreasing PNM seen during the 13-year study period, the results were analysed in three time periods. The PNM in the 24 counties showed no linear correlation with the CS rate (Fig. 1). Each mark (=county) represents about 130 twins and about 11 deaths. These relatively small numbers account for the considerable variation in PNM rates found in all three periods studied. Therefore the change in CS rate within in each county in the three periods was evaluated against the change in PNM. If a decrease in PNM was causally related to an increase in CS rate (meaning that a larger increase in CS rate would lead to a larger decrease in PNM), the correlation coefficient between these two parameters should have been negative, but a positive correlation coefficient was found.

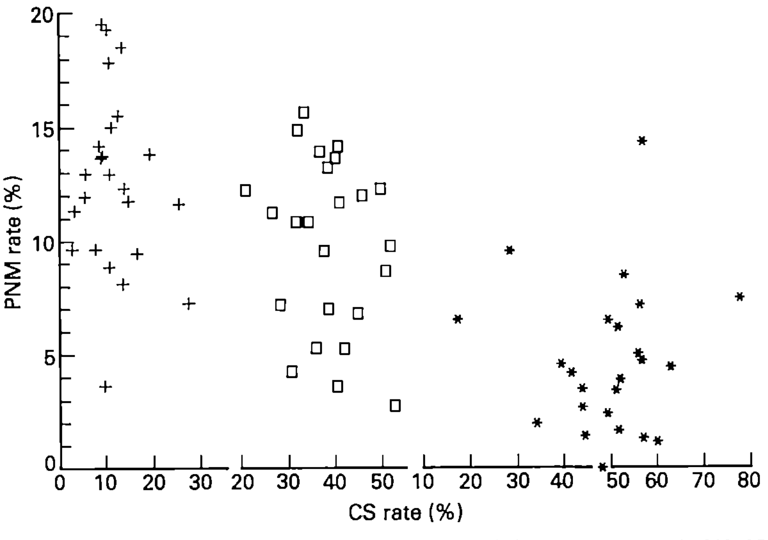

Fig. 1. Perinatal mortality (PNM) rates for 1973–76 (+), 1977–81 □, and 1982–85 (*), in relation to caesarean section (CS) rates in all 24 counties. No association was found between the different CS rates and the PNM figures.

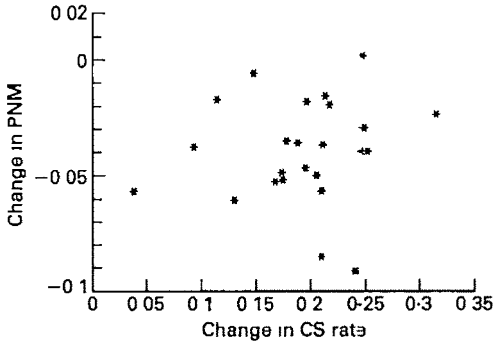

Fig. 2. No association ($r = 0{\cdot}11$) was found between changes in the caesarean section (CS) rate and perinatal mortality (PNM) when the change was expressed as the regression coefficient for a straight line, adjusted to the rate found in each of the three periods Thus, the marks should be scattered around a line from top left to low right if the hypothesis were true that an increase in the CS rate was causally associated with a decrease in the PNM (negative correlation coefficient). Each mark represents one county.

When analyzing the time for operation during the day, a sharp increase of the CS rate was found between 08.00 and 13.00 hours (an almost threefold increase). The CS rate was stable during the rest of the day. The reason for this peak is not known, though one may speculate that planning of the abdominal delivery, even if an emergency CS is performed, might be the main factor. As only low-birthweight twins were included in the study, the number of elective CS ought to be low. A lower PNM rate for twins born abdominally was seen between 07.00 and 13.00 hours, but also between 17.00 and 01.00 hours when the CS rate was stable. This indicates that other factors than a high CS rate influenced mortality figures. One may speculate that the comparatively higher PNM for twins born between 02.00 and 05.00 hours might be due to an insufficient perinatal management during these early hours. However, some caution is needed in the interpretation of the results. Most of the sections were made during the latter part of the study period, whereas most of the perinatal deaths occurred during the first half.

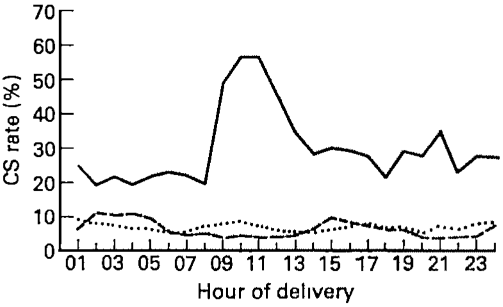

Fig. 3. No association was found between changes in the caesarean section (CS) rate during the day, and perinatal mortality (PNM) figures. ———, CS rate; ……. PNM (moving average) for twins born vaginally, – – – –, PNM (moving average) for twins born by CS

It is well known that second twins have a higher PNM rate than first twins, and it has been suggested that CS might improve fetal outcome (Ware 1971). With an increasing CS rate a trend was found with improved second twin prognosis (a reduced ratio), but the trend was not statistically significant. During the years with a stable CS rate, the highest as well as the lowest PNM rate was seen, indicating that other factors than CS were responsible for the most of the changes in PNM.

The most important causes of PNM for preterm fetuses are related to immaturity. In contrast, in the term period, factors like pre-eclampsia, deformity, trauma or maternal disease are said to contribute significantly to PNM (Campbell & MacGillivray 1988). Therefore, it is not possible to extrapolate the conclusions from the present study for twins weighing ≥2 500 g at birth.

To sum up, there was no causal relation between the delivery route and the improved prognosis for low-birthweight twins. Factors other than the increase in the CS rate may be responsible for the major part of the declining PNM rates. It is possible that the regionalization

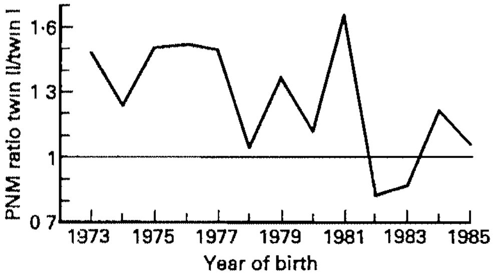

Fig. 4. No association was found between the ratio perinatal mortality (PNM) twin II/twin I and an increasing caesarean section rate (as shown in Table I).

of perinatal care, better techniques for fetal monitoring and currently improving neonatal care might have a greater impact on PNM. It has also been suggested that a reduction in neonatal deaths from respiratory distress syndrome has had a greater impact on the PNM in recent years than has the mode of delivery (Bell *et al.* 1986).

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Caesarean section for the birth of the second twin

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Summary. Twin pregnancies delivered after 28 weeks gestation between 1980 and 1988 were reviewed. Of 510 twin pregnancies, 184 (36%) were delivered by caesarean section. There were 22 (4·3%) combined vaginal/abdominal deliveries which comprised 12% of the 184 twin pregnancies delivered by caesarean section. Persistent transverse lie or a high breech presentation was the commonest indication for caesarean section for the second twin.

Twin pregnancy is associated with increased perinatal mortality (McCarthy *et al.* 1981) which is largely due to the increased frequency of preterm birth and low birthweight infants (Hawrylyshyn *et al.* 1982). Vaginal birth of the first twin is no guarantee of safe passage for the second twin, particularly should the latter be the larger. As malposition or malpresentation of the second twin is a frequent occurrence (Farooqui *et al.* 1973; Guttmacher & Kohl 1958; Kurtz *et al.* 1955), there may be higher morbidity and increased risk of caesarean section if the birth of the second twin is not managed appropriately and skilfully. Recently, an increasing trend in caesarean section for the second twin has been noted (Rattan *et al.* 1986; Constantine & Redman, 1987).

To define the reasons necessitating caesarean section for the second twin after vaginal birth of the first twin, we conducted a retrospective study of all twin pregnancies delivered after 28 weeks gestation at the Birmingham Maternity Hospital in the 9-year period between January 1980 and December 1988.

Subjects and methods

Maternal records of all twin pregnancies where the first twin was born vaginally and the second by caesarean section (combination delivery) were selected for this report. Details on parity, gestation, indication for combination delivery, interval between births, Apgar scores, mode of anaesthesia, birthweight and perinatal outcome were reviewed.

Results

There were 510 twin deliveries during this study period, of which 184 (36·1%) were delivered by caesarean section; 22 of these (12%) were combination deliveries (4·3% of the 510 twin deliveries). The overall rates of combination delivery were: 2·4% (1/42) in 1980, 1·6% (1/62) in 1983, 7·8% (5/64) in 1984, 8·6% (5/58) in 1985, 5·8% (3/51) in 1986, 5·2% (3/58) in 1987 and 7·4% (4/54) in 1988. There were no combination deliveries recorded in 1981 and 1982. The primary indications for caesarean section in these 22 combination deliveries are shown in Table 1

In these 22 combination deliveries, 15 women had epidural analgesia for the birth of the first twin and the other seven had local analgesia. In 14 pregnancies the birth of the first twin was managed by a registrar, seven were managed by midwives and one by a senior registrar. In 21 deliveries, the senior registrar was called only after the birth of the first twin. The birth of the second twin was eventually managed by the senior registrar in 17 women and by the registrar

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Table 1. Primary indication for using caesarean section for the birth of the second twin

Indication	No	Maternal age (years)	Parity	Gestation (weeks)	Birthweight (kg)	Apgar score 1 min	Apgar score 5 min	Interval between births (min)
Transverse lie/high breech	1	23	0	39	2·94	8	10	51
	2	25	0	40	3·04	5	8	23
	3	27	0	38	3·16	5	9	21
	4	30	1	38	2·63	8	9	68
	5	37	8	37	2·78	8	9	61
	6	34	1	38	3·44	9	10	30
	7	28	0	34	2·41	9	9	47
	8	21	0	33	2·22	7	9	18
	9	22	1	39	2·24	6	9	29
	10	23	0	31	1·90	4	9	50
	11	31	0	40	3·12	9	9	23
	12	27	3	36	2·07	5	9	17
Compound presentation	13	23	1	37	3·08	9	9	50
	14	31	3	39	3·23	9	10	38
	15	33	0	32	1·72	8	10	18
	16	29	1	39	2·48	9	10	20
Contracted cervix	17	17	1	29	1·27	5	8	33
	18	37	3	35	2·30	3	5	81
Brow presentation	19	28	0	39	2·18	8	9	42
Shoulder presentation	20	32	0	30	1·60	3	8	19
Fetal distress/ placental abruption	21	32	2	35	2·76	8	10	36
Fetal distress/failed breech extraction	22	26	1	31	1·55	7	9	16

in the other five. All were delivered under general anaesthesia. Five of the combination deliveries occurred between 09.00 and 17.00 hours, two between 17.00 and 23.00 hours and 15 between 23.00 and 09.00 hours.

In four of the 22 combination deliveries, the first twin born vaginally weighed more than 3 kg and five of the second twins born by caesarean section weighed more than 3 kg. In only one case was the second twin more than 500 g heavier than the first. There were no intrapartum or neonatal deaths in these 22 combination deliveries.

Discussion

Our report describes the largest series of combination deliveries in which the second twin was born by caesarean section after vaginal birth of the first twin. Indications for caesarean section of second twins include cephalopelvic disproportion, brow presentation, face presentation, compound presentation, contracted cervix unresponsive to oxytocic augmentation, presence of uterine rupture, and failed extraction. In some circumstances indications may also include fetal distress, cord prolapse and placental abruption. However, in the present series, persistent transverse lie or a high breech presentation was the most common indication for caesarean section for the second twin (55%). An important question is why there was no attempt at manipulation of the second twin before resorting to caesarean section.

Both intrapartum external version (Chervenak *et al.* 1984) and breech extraction (Acker *et al.* 1982) of second twins have been shown to be safe procedures. If the cervix remains fully dilated and analgesia is adequate, such obstetric manoeuvres can be attempted by experienced obstetricians. In the present series, of the 22 combination deliveries 17 occurred between 17.00 and 09.00 hours when experienced obstetricians may not be immediately available. In 21 cases, the experienced obstetrician was called only after the birth of the first twin. The intervals between the births of the twin babies ranged from 16 to 81 min. A prolonged delivery interval, and especially when the cervix contracts down, will leave the attending obstetrician little option but to perform a caesarean section. If experienced personnel are summoned in time for the birth of the first twin, this would allow trainees to gain supervised practical experience in operative vaginal techniques and it may possibly minimize the use of caesarean section for the birth of the second twin.

In face of the decline in popularity of version of singleton breech (Bradley-Watson 1975; Berg and Kunze 1977) the increased use of caesarean section for singleton breech (Rovinsky *et al.*

1973; Duignan 1980) and twin pregnancy (Taylor 1976; Certrulo *et al.* 1980), trainees have fewer opportunities to gain practical experience of obstetrical manoeuvres and vaginal twin deliveries. Emphasis on safe delivery of a precious fetus, coupled with the potential threat of litigation, may also lead to an increase in caesarean sections in general (Notzon *et al.* 1987; Shino *et al.* 1987; Lomas 1988).

In conclusion, we observed an increased use of caesarean section for the birth of second twins. However, the present report does not permit conclusions about the perinatal morbidity associated with combination delivery in twin pregnancy.

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Socio-economic and ethnic factors in stillbirth and neonatal mortality in the NE Thames Regional Health Authority (NETRHA) 1983

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Summary. All stillbirths and neonatal deaths occurring in the North East Thames region were studied in 1983. This report describes the socio-economic and ethnic differences in that cohort. The stillbirth and neonatal mortality rates of babies born to fathers of social class V (16·8 per 1000 total births) was almost double that of social class I fathers (8·6 per 1000 total births). The most marked social class gradient was seen in the macerated stillbirth groups. Of particular concern was the extremely high stillbirth and neonatal mortality rate for women born in the Indian subcontinent. This was most evident in Pakistani women who had a stillbirth plus neonatal mortality rate of 17·3 per 1000 total births, almost twice that of the women born in the UK (9·0 per 1000 total births). Again, as with social class, macerated stillbirths appeared to contribute disproportionately to the excess mortality. Mortality rates were aggregated into four birthweight specific groups. Asian women had higher mortality rates in the higher birthweight groups, whereas in the lower birthweight group their babies did slightly better. This study indicated that the special needs for working class and ethnic minority mothers within NE Thames were not being met, and the Regional Health Authority was strongly recommended to review services to these groups.

Perinatal mortality is widely used as an indicator of the health of a population and the effectiveness of the health services. The high perinatal mortality rate (PNMR) of England and Wales compared with other developed countries has caused considerable concern in recent years (House of Commons Social Services Committee 1980). Perhaps of even greater concern has been the wide variations in PNMR observed between different health regions in England and Wales, the worst having a perinatal mortality rate 30% higher than the best (OPCS 1987*a*).

For several years, the fall in the PNMR in North East Thames Regional Health Authority (NETRHA) has been roughly parallel with that observed in England and Wales (Fig 1). Nevertheless, until 1985 PNMR in NETRHA remained considerably higher than that seen in several other health regions, notably its neigh-

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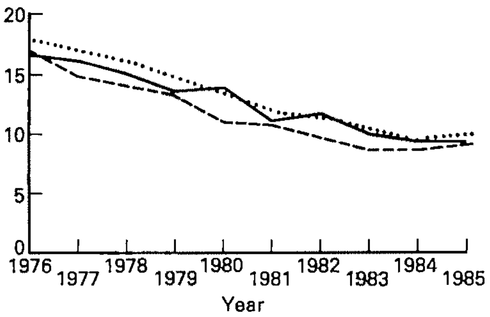

Fig. 1. Perinatal mortality rates per 1000 live births between 1976 and 1985, NE Thames Region (———), NW Thames Region (– – –); England & Wales (. .). Source· OPCS DH3 Series.

bour, North West Thames. Comparison between these two regions reveals that NETRHA has a relative excess of births to women who are not married to the baby's father, highly parous women (parity ⩾ 4) and low social class families (social classes IV and V) (OPCS 1985). Examining the perinatal mortality of these groups with adverse sociobiological factors in 1983, it is clear that NE Thames babies suffer a double disadvantage. Not only is there a greater incidence of adverse risk factors, but also within each group the stillbirth rate (SBR), PNMR or neonatal deaths rate is up to 70% in excess of that observed in NW Thames (Fig. 2).

Analysis also reveals marked differences in mortality rates between districts in the region in 1985, ranging from 7·1 per 1000 total births in Hampstead to 11·3 in City and Hackney (OPCS 1987 *b*).

In response to concern about the above issues, the Regional Health Authority established a Perinatal Review Working Party in 1980, with membership drawn from obstetrics, paediatrics, midwifery, community medicine, general practice and pathology, which conducted a special survey to investigate the causes of stillbirth and neonatal death in NETRHA during 1983. This account presents the regional stillbirth and neonatal mortality rates by social class and ethnic group.

Methods

The cases were identified from stillbirth certificates and death certificates of babies aged ⩽4 weeks. Stillbirths and neonatal deaths were studied rather than perinatal deaths because neonatal intensive care units are increasingly able to keep some of these babies alive beyond the first week of life. These certificates were obtained from the Office of Population Census and Surveys (OPCS) and allowed calculation of mortality rates within the Region. Deaths occurring to non-residents were excluded from the survey. Where possible, maternity records for the units in NE Thames were checked, and it seems that ascertainment of deaths within the Region was virtually complete. Deaths of babies of residents occurring outside the Region could not be checked.

Clinical data were obtained by requesting the completion of a questionnaire for each stillbirth and neonatal death. Initially the clinicians in the unit where the death had occurred were approached, and then if the baby had been transferred after birth the clinicians in the unit where the birth occurred. In some cases, the form was completed from the clinical notes by one of the authors. Some clinical information was obtained in 95% of deaths.

The questions asked included occupation of father, which was coded by the Registrar General's classification, and birthplace of mother, which was coded by the OPCS classification used in the decennial census. The ethnic group of the mother was also recorded. Classification of cause of death was as suggested by Wigglesworth (1980), because cases are subdivided into groups with clear implications for clinical management.

Mortality rates (stillbirths and neonatal deaths) by social class were calculated by dividing the deaths in each social class group by the total number of births to fathers from that social class group resident in NETRHA in 1983 (OPCS 1985). Numerator data were taken by clinicians from medical records while denominator data were taken by OPCS from birth registrations. This may introduce some disparity in the calculation of mortality rates.

Mortality rates (stillbirths and neonatal deaths) by mother's country of birth were calculated by dividing the deaths in each group by the total number of births to mothers born in that country resident in NETRHA in 1982 (OPCS 1983). No comparable denominator is available by ethnic group. As with social class, there may be some discrepancy between the source of numerator data (medical records) and denominators (death certificate).

The collection of clinical data in this study

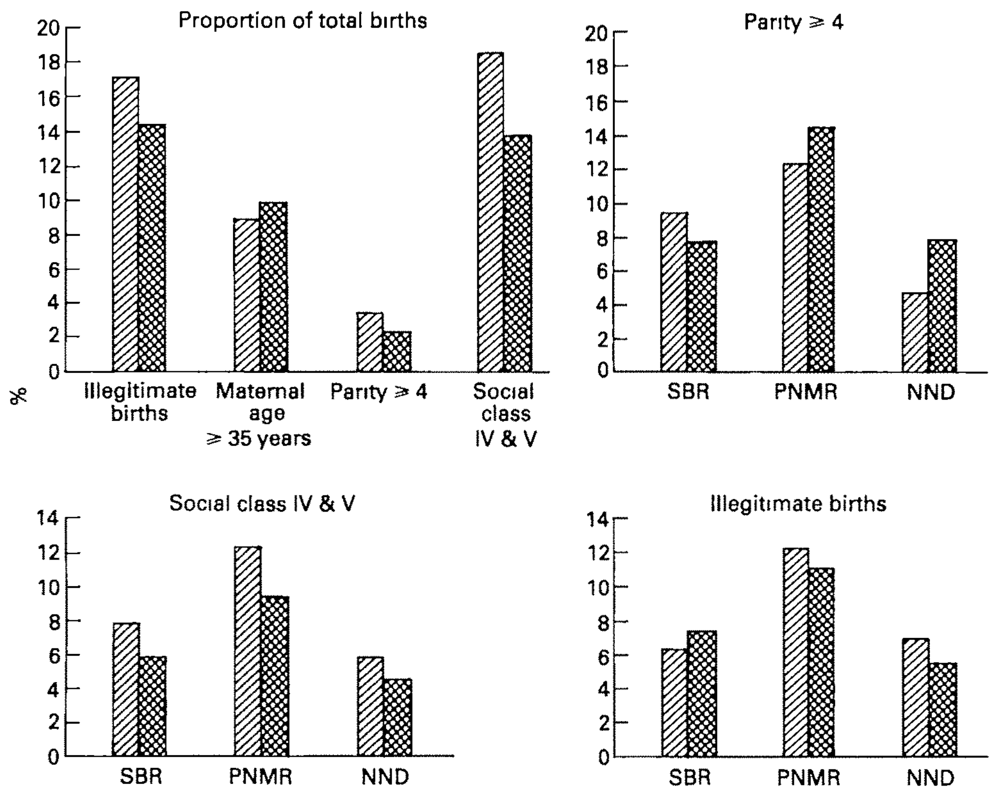

Fig. 2. Mortality rates by sociobiologic factors, NE Thames ▨ and NW Thames ▩ regions, 1983 The stillbirth (SBR) and perinatal mortality rates (PNMR) are shown per 1000 total births and the neonatal death rate (NND) per 1000 live births Source: OPCS DH3 85/2

allowed comparison of ethnic origin with country of birth.

It was also possible to calculate the birthweight-specific mortality rates (stillbirths and neonatal deaths) per 1000 total births in residents of North East Thames. As the numbers in some groups were very small, the birthweights were aggregated into four groups: very low (< 1500 g), low (1500–2499 g), normal (2500–3999 g) and high (≥4000 g).

Results

There were 541 stillbirths and neonatal deaths identified in 1983 by the NETRHA survey. This compares favourably with the 543 deaths reported by OPCS (1985). The results of the survey are reported in full elsewhere (NETRHA 1985) and only those relating to social class and mother's country of birth are included here.

Mortality rates (stillbirth and neonatal deaths) by social class

Mortality rates (stillbirth and neonatal deaths) by father's occupation were recorded in over 90% of cases with a further 10% categorized as unemployed or 'other'. The stillbirth and neonatal mortality rates among babies born to fathers of social class V (16·8 per 1000 total births) was almost double that for fathers of social class I (8·6 per 1000 total births). The most marked social class gradient was seen in the macerated stillbirth group (Table 1), where the relative risk for social class V compared with social class I was 6·5. Of interest is the reversal of the normal social class gradient between social class III M (manual) and III N (non-manual) where the relative risk was 2·5.

Birthplace of mother as proxy for ethnic group

In this survey, the mother's place of birth as recorded on the birth certificate has been used as a proxy for ethnicity. Table 2 shows the cross-tabulation of birthplace of the mother with her ethnic origin as recorded by the clinicians in the survey. Of the women born in the UK 5% were said to have a different ethnic origin, while 0·5%

Table 1. Stillbirths (SB) and neonatal death (NND) rates in NE Thames (residents only) in 1983 by social class of father per 1000 total births

	Social class														
	I		II		IIIN		IIIM		IV		V		Others	Not known	All
	n	(rate)	*n*	(rate)	*n*	(rate)	*n*	(rate)	*n*	(rate)	*n*	(rate)	*n*	*n*	*n*
Macerated stillbirths	7	(2·4)	18	(1·8)	18	(3·6)	48	(3·3)	28	(4·6)	12	(6·3)	18	17	166
Congenital malformation	7	(2·4)	21	(2·1)	11	(2·2)	32	(2·2)	12	(2·0)	7	(3·7)	15	7	112
Asphyxia	4	(1·4)	21	(2·1)	17	(3·4)	26	(1·8)	15	(2·5)	5	(2·6)	15	13	116
Immaturity	4	(1·4)	21	(2·1)	14	(2·8)	23	(1·6)	13	(2·1)	4	(2·1)	13	9	101
Other causes	3	(1·0)	9	(0·9)	4	(0·8)	9	(0.6)	6	(1·0)	4	(2·1)	4	7	46
Total births	2900		10 000		5000		14 400		6100		1900				51 527
Total deaths	25		90		64		138		74		32		65	53	541
Rate	8·6		9·0		12·8		9·6		12·1		16·8				10·5

Source Rates were calculated from the number of SBs and NNDs occurring in the survey to fathers of each social class and the total number of births to fathers of the social classes resident in NE Thames in 1983 obtained from OPCS DH3 85/2.

The SB and NND rate for residents of NETRHA in 1983 was 10·8 per 1000 total births recorded in OPCS Monitor DH3 85/2. This represents 543 deaths compared with the 541 identified in the survey of the Caucasian mothers recorded their country of birth as elsewhere. The 'second generation effect' was most marked for families of West Indian origin.

Mortality rates (stilbirth and neonatal deaths) by birthplace of mother

The mother's place of birth was recorded in 90% of cases. Overall 75% of the births in 1983 were to women born in the UK compared with 65% of the deaths, and 8% of the births were to women born in the Indian subcontinent, compared with 11% of the deaths.

Infants whose mothers were born in the UK had the lowest mortality rate (9·0 per 1000 total births). Of particular concern are the extremely high rates of stillbirth and neonatal death to mothers who were born in the Indian subcontinent. This was most evident in Pakistanis who had a stillbirth plus neonatal mortality rate of 17·3 per 1000 total births. Again, as in the social class analysis, macerated stillbirths appeared to contribute disproportionately to the excess mortality (Table 3). The relative risk of a macerated stillbirth was 1·7 for Irish women and 2·0 for Pakistani women.

Birthweight—specific mortality rates

The aggregated birthweight-specific mortality rates (stilbirths and neonatal deaths) in NE Thames in 1983 by birthplace of mother are shown in Table 4. The numbers of deaths are very small but there are higher rates in the Asian women in the higher birthweight groups. Interestingly, at low birthweight (1500–2499 g) and very low birthweight (<1500 g), Bangladeshi babies seem to do slightly better.

Discussion

National data on perinatal mortality are now very good, but regional studies offer the opportunity to examine the associations between social and clinical factors at greater depth. One interesting finding was that, in this study, country of birth represents a good proxy for ethnic origin. Only 5% of mothers born in the UK were not of Caucasian ethnicity. This may reflect a high proportion of more recent immigrants in this population.

Some of the poorest inner city areas in the country are in NETRHA, and a relatively large proportion of the population of these areas

Table 2. Cross-tabulation of birthplace of mother and ethnic origin for stillbirths and neonatal deaths in NE Thames

	Ethnic origin of mother								
Birthplace of mother	UK	Eire	West Indies	India	Pakistan	Bangladesh	Cyprus	Other	Total
UK	349 (69·8)	0	11 (2·2)	2 (0 4)	1 (0 2)	0	0	4 (0·8)	367 (73·4)
Eire	1 (0·2)	9 (1·8)	0	0	0	0	0	0	10 (2)
West Indies	0	0	13	0	0	0	0	0	13 (2 6)
India	0	0	0	19 (3 8)	0	0	0	0	19 (3 8)
Pakistan	0	0	0	0	21 (4 2)	0	0	0	21
Bangladesh	0	0	0	0	0	23 (4·6)	0	0	23
Cyprus	0	0	0	0	0	0	5 (1)	0	5
Other	1 (0·2)	0	0	3	1	0	0	37 (7·4)	42 (8 4)
Total	351 (70·2)	9 (1·8)	24 (4·8)	24 (4·8)	23 (4·6)	23 (4 6)	5 (1)	41 (8 2)	500 (100)

Source: Ethnic origin of mother was obtained from the survey while birthplace of mother was recorded on the birth certificate of the infant.

Date were missing from 41 cases Values are numbers of women with percentages in parentheses.

Table 3. Stillbirth (SB) and neonatal death (NND) rates in NE Thames (residents only) in 1983 by birthplace of mother per 1000 total births

	UK		Eire		West Indies		India		Pakistan		Bangladesh		Others	Not known	All
	n	(rate)	*n*	(rate)	*n*	(rate)	*n*	(rate)	*n*	(rate)	*n*	(rate)	*n*	*n*	*n*
Macerated stillbirths	117	(3·1)	6	(6·0)	1	(0·9)	2	(1·5)	10	(8·7)	6	(3·8)	21	3	166
Congenital malformation	73	(1·9)	4	(4·0)	3	(2·6)	5	(3·6)	5	(4·3)	3	(1·9)	12	7	112
Asphyxia	80	(2·1)	0	(0·0)	2	(1·7)	4	(2·9)	5	(4·3)	8	(5·0)	7	10	116
Immaturity	61	(1·6)	1	(1·0)	7	(6·0)	4	(2·9)	0	(0·0)	0	(0·0)	5	23	101
Other	20	(0·5)	2	(2·0)	0	(0·0)	3	(2·2)	0	(0·0)	5	(3·1)	4	10	46
Total births	38 873		966		1208		1366		1161		1757				51 527
Total deaths	351		13		13		18		20		22		49	55	541
Rate	9·0		13·5		10·8		13·2		17·2		12·5				10·5

Rates were calculated from the number of SBs and NNDs occurring in the survey for each group of mothers and the total number of births occurring during 1983 to those mothers who were resident in NE Thames (from Immigrant Births Table IB5(A) 1983 available from OPCS). The total number of births given in these tables differs from those given in OPCS DH3 85/2 because the Immigrant Birth Tables contain livebirths only

The SB and NND rate for residents of NETRHA in 1983 was 10·8 per 1000 total births recorded in OPCS Monitor DH3 85/2.

Table 4. Aggregated birthweight-specific mortality rates (stillbirths and neonatal deaths) per 1000 total births in NE Thames (residents only) in 1983 by birthplace of mother

	Birthweight groups (g)									
	<1500		1500–2499		2500–3999		≥4000		Total	
Birthplace of mother	Total births	Death rate	Total births	Death rate	Total births	Death rate	Total births	Death rate	Total births	Death rate
UK	337	326·3	2323	42·6	32 806	3·4	3296	4·0	38 873	9·0
Eire	10	500	63	95·2	785	2·5	107	0	966	13·5
West Indies	27	333	104	9·6	1108	3·0	63	0	1208	10·8
India	13	538	149	26·8	1155	6·1	49	0	1366	13·2
Pakistan	16	375	88	68·2	989	7·1	67	14·9	1161	17·2
Bangladesh	11	273	155	45·2	1516	7·9	71	0	1757	12·5
Total births	542		3324		43 562		4040		51 527	
Total deaths	170		122		155		14		541	
Rate	314		37		3·6		3·5		10·5	

belong to ethnic minority groups and social class IV and V. For instance, in Hackney, over 44% of the population are estimated to come from black and ethnic minority groups (Howe 1985). Sociobiological factors such as social class, maternal age and parity are well-recognized determinants of perinatal mortality (Butler & Bonham 1963). More recently, attention has been drawn to the high mortality rates of certain groups of immigrants to this country (Marmot *et al.* 1984) Babies, unfortunately are no exception Nationally, the stillbirth rate for women born in Pakistan is nearly 50% higher than that for women born in the UK (OPCS 1986).

The difference in stillbirth and neonatal death rates between social classes and ethnic groups is most marked in the macerated stillbirths and congenital malformations (Tables 1 & 3). The numbers in this study are small but the twofold rise in relative risk across social classes and the high mortality rates in babies of women born in Pakistan and Eire are consistent with national rates (OPCS 1986). Macerated stillbirths represented the largest single group of deaths in the study ($n = 166$), accounting for 30% of all deaths and 60% of stillbirths (NETRHA 1985). Women born in Pakistan and Eire had the highest rates, although the latter must be interpreted with caution because of the small numbers.

Women born in Pakistan and Eire also have high rates of congenital malformations. Overall in the study, congenital malformations were recognized as responsible for death in 112 infants of whom 30 (27%) were stillborn.

The importance of early antenatal attendance is well known, yet over 30% of the mothers of the babies who died from congenital malformation made their first antenatal visit after 16 weeks gestation. Only a third presented before 12 weeks (NETRHA 1985). The numbers were too small to analyse gestation at booking by the mother's country of birth. Data from a maternity census carried out as another part of the NETRHA perinatal review indicate that, in many cases, the hospital itself may have contributed to the delay In eight hospitals the interval between referral and first visit was ≥3 weeks and six of the hospitals apparently considered this delay to be quite acceptable (NETRHA 1983) Antenatal care has perhaps the most to offer to those women who are at risk of developing complications. The extremely high incidence both of macerated stillbirth and other causes of perinatal death observed in this survey amongst infants of social classes IV and V of mothers born in Pakistan must call into question whether the special needs of these groups of the population are being adequately met by the health services of the region. It cannot be assumed that screening or termination will be refused on the grounds of religious or personal beliefs. Women must be appropriately counselled so that they can assess their individual risk and choose how to deal with it.

Clearly improvement in social conditions would most benefit the health of these groups, but in the absence of any influence over these factors, the working party recommends that the North East Thames Regional Health Authority reviews the provision of services for non-English speaking women and ensures that effective antenatal care is given to women at greatest risk.

The working party has continued to collect data about stillbirths and neonatal deaths. Clinical data are limited compared with the 1983 survey, but some information will soon be available on deaths from 3 years (1983–1985) which will allow greater confidence in the analysis of birthweight–specific mortality (stillbirths and neonatal death) rates.

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A histological and immunohistological study of cervical intraepithelial neoplasia in relation to recurrence after local treatment

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Summary. A retrospective histological study was performed on 23 patients who had presented with recurrent cervical intraepithelial neoplasia (CIN) 18 months or more after apparently adequate local destructive treatment and a comparable control group of 23 patients who had no recurrence at 18 months. All recurrences were in women with CIN 3. Detailed examination of pretreatment biopsies showed that there were significant differences in both the extent of crypt involvement ($P<0{\cdot}01$) and maximum depth of CIN ($P<0{\cdot}01$) between the recurrent groups and the comparison group of women without recurrence. There was also a significant difference in mitotic count between the two groups ($P<0{\cdot}01$). Immunocytochemical staining for Langerhans' cells or human papilloma virus common antigen showed no significant difference between the two groups. A mitotic count of 35 per ten high-power fields or a depth of crypt involvement >1·7 mm in the pretreatment biopsy was invariably associated with recurrence and identified 13/22 (59%) cases of recurrent disease. The histological reporting of these features may be of value in predicting a group of women at high risk of recurrence of CIN after local treatment.

The current practice in the treatment of cervical intraepithelial neoplasia (CIN) is towards conservative and local methods such as cryotherapy, electrodiathermy, laser vaporization and cone biopsy (Singer & Walker 1985). The safe use of these methods depends on accurate diagnosis of the severity and extent of the lesion and on the exclusion of invasive disease (Anderson & Hartley 1980). The primary treatment is successful in from 60% to 90% of women depending on the method used (Singer & Walker 1985). In a minority of women further treatment is required either because of inadequate clearance or because of recurrence of CIN which may happen many years after apparent initial cure The factors influencing the likelihood of recurrence are poorly understood.

Currently the detection of recurrence depends on cervical cytology, repeat colposcopic examination and biopsy, although follow-up practices may vary from centre to centre. The identification of a group of women at high risk of recurrence who might need close scrutiny or more extensive local treatment would help both to improve the service to patients and assist in the

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organization of busy colposcopy clinics and cytology departments. A retrospective histological study was performed on the pretreatment colposcopic biopsies of patients who had presented with recurrent CIN more than 12 months after apparently adequate treatment.

Subjects and methods

Subjects were selected from patients undergoing follow-up after treatment of CIN in the Islington District Colposcopy Clinic between July 1981 and March 1986. After treatment, all the patients had received colposcopic and cytological examination at intervals of 4 months for 12 months and had then been followed up by annual cytological examination. Recurrence was defined as the presence of histologically proven CIN at least 12 months after initial treatment, or after an apparently complete cone biopsy. Twenty-three patients were identified, all of whom had recurrent CIN 3, 22 after a disease-free period of ≥12 months and one only 3 months after complete histological and clinical clearance by cone biopsy

A control group of 23 patients was selected from the next clinic attenders with CIN 3 to receive similar treatment and who had been followed up for at least 18 months. The median age of each group was 34 years (range 21–44 years for those with recurrent CIN and 21–47 years for the control group) Six patients in each group had a cone biopsy and the remainder were treated by laser vaporization or electrodiathermy.

Histological examination

The biopsies obtained at first presentation were studied retrospectively without knowledge of the final outcome. For the patients treated by laser vaporization or diathermy, colposcopic biopsies obtained using Eppendorf forceps were available. The biopsies had been fixed in formol sublimate solution and each specimen had been sectioned at three levels perpendicular to the surface. Each section was 4μm thick and was stained with haematoxylin and eosin. For the six patients in each group who had been treated by cone biopsy, radical sections of the cone were examined; about 12 sections from each patient were available for study.

The histological features studied are listed in Table 1. Human papillomavirus (HPV) infection was diagnosed using the criteria of Jenkins *et al.* (1986) and Dyson *et al.* (1984). CIN was graded according to the criteria of Buckley *et al.* (1982). All specimens were graded as CIN 3. The depth of crypt involvement by CIN was measured as the perpendicular distance in millimetres from the surface of the overlying superficial epithelium to the deepest point of crypt involvement. A stage micrometer was used for this measurement. The extent of crypt involvement was graded on a semi-quantitative scale of minimal, moderate and extensive: minimal was involvement of the upper third of less than three crypts; moderate was involvement of more than half of the depth of up to four crypts, extensive was deep involvement of more than four crypts.

A 10 × 10 eye-piece micrometer was used to count the numbers of mitoses. The grid defined single high-power fields (h.p.f) with an area of 1·02 mm^2 with the ×25 objective lens on the microscope used. The number of metaphase mitoses, normal and abnormal, in ten such fields was counted for each case (mitotic count/10 h.p.f.).

Mononuclear cell inflammatory infiltration was graded as mild, moderate or heavy Mild infiltration was defined as the presence of a small number of lymphocytes, plasma cells and histiocytes in the subepithelial connective tissue. Moderate infiltration was diagnosed when larger numbers of chronic inflammatory cells were present, and heavy mononuclear cell infiltration when the stroma was densely packed with lymphocytes, plasma cells and other cells. No sections showed a significant acute inflammatory component and there were no examples of follicular cervicitis

Immunocytochemistry

Expression of HPV antigen was studied in paraffin-embedded sections from the initial

Table 1. Histological and immunocytochemical features studied

The maximum depth of crypt involvement by CIN.
The extent of endocervical crypt involvement by CIN.
Mitotic count.
The presence of endocervical glandular cell atypia
The presence and amount of subepithelial mononuclear cell infiltrate
Histological evidence of HPV infection.
Immunocytochemical staining for HPV common antigen and S100 antigen positive Langerhans' cells.

biopsy using the peroxidase–antiperoxidase (PAP) method. Wax was removed in xylene, the sections transferred to alcohol and exposed to endogenous peroxidase blocked with 0·5% hydrogen peroxide in methanol solution. Sections were rehydrated in Tris buffered saline (pH 7·4) solution and then incubated for 1 h with primary antiserum raised in rabbit against a genus-specific bovine papillomavirus antigen (Dako B580) at 1/300 dilution. After two washes in Tris buffered saline solution sections were incubated with swine antirabbit antiserum at 1/55 dilution for 1 h, and then with peroxidase–antiperoxidase complex (Dako) at 1/200 dilution for 1 h. All incubations were performed in a humidified chamber. The peroxidase reaction was developed in freshly prepared 0·5% 3,3-diaminobenzene in 0·01% hydrogen peroxide solution and the sections were counterstained with haematoxylin.

Sections known to be positive for HPV antigen were used as positive controls. Duplicate sections from the patients studied were incubated with normal rabbit serum instead of anti-HPV serum as negative controls.

S100 positive Langerhans' cells were demonstrated in paraffin sections using the immunoperoxidase method as described previously (Tay *et al.* 1987a).

Statistical analysis

The significance of the difference in the mean depth of CIN and of mitotic count between the study group and controls was tested using Student's unpaired *t*-test after log transformation of the data to normalize the distribution. Comparisons between the two groups in respect of the other histological features studied was performed using the χ^2-test for trend

Results

The mean interval between treatment and recurrence was 28·25 months (range 3–116 months). In the one patient with recurrence at <1 year after treatment there had been complete excision by cone biopsy. The mean interval to recurrence after treatment for each mode of treatment was 27 months for diathermy, 26·5 months for laser evaporation and 47 months for cone biopsy.

All the patients with recurrent CIN had CIN 3 on the original biopsy. None of the cases or controls showed any glandular atypia. The original biopsy of one patient was inadequate for assessment beyond the grade of CIN, and was therefore excluded from further analysis. The recurrence could be of any grade, although most (16/23) were CIN 3. Grade at recurrence did not appear to be related to mode of treatment. The major histological findings in the recurrent and controls groups are summarized in Table 2.

There were highly significant differences in both the extent of crypt involvement ($\chi^2 = 9{\cdot}5$; $P<0{\cdot}01$) and the maximum depth of CIN ($t = 2{\cdot}8$; $P<0{\cdot}01$) between the recurrent and non-recurrent groups. There was also a highly significant difference in mitotic count between the two groups ($t = 2{\cdot}7$; $P<0{\cdot}01$). The association of recurrent CIN with a depth of CIN >1·7 mm was significant ($\chi^2 = 5{\cdot}1$; $P<0{\cdot}05$) and that with a mitotic count >35 mitoses/10 h.p.f. highly significant ($\chi^2 = 9{\cdot}2$; $P<0{\cdot}005$). The presence of either risk factor also showed a highly significant association ($\chi^2 = 7{\cdot}5$; $P<0{\cdot}01$) including 13 of the 22 with recurrence (59%) but none in the control group.

The mitotic count and the maximum depth of involvement are plotted in Fig. 1. There was no significant statistical correlation between mitotic count and maximum depth of involvement ($r = 0{\cdot}265$). The plot shows that a mitotic count in excess of 35 mitoses/10 h.p.f. and a maximum depth of involvement >1·7 mm were always associated with recurrence.

The search for a subset of Langerhans' cells by S100 staining revealed very little positive staining in either group. Histological or immunocytochemical evidence of HPV infection was found in a similar proportion of each group. There was no difference in the frequency of HPV infection between the first and second biopsies of patients in the recurrent group.

Discussion

Recurrence in a group of patients with CIN 3 was associated with the extent and depth of crypt involvement and with the mitotic count. No differences were found in the prevalence of HPV infection as judged by histology or by HPV common antigen staining.

The definition of recurrence used was chosen to exclude immediate failure of ablative therapy to remove all detectable disease. Complete removal of disease verified histologically and/or a disease-free period as shown by colposcopic

Table 2. Results of histological assessment

	Recurrent CIN (n=22)	Control (n=23)
Mean maximum depth of crypt involvement by CIN (mm) (range)	1·16 (0·3–3·0)	0·58 (0·2–1·6)
Endocervical crypt involvement n (%)		
Minimal	9 (41)	20 (87)
Moderate	8 (37)	3 (13)
Extensive	5 (25)	0
Mean mitotic count as metaphase mitoses/10 h.p f (range)	24·8 (5–110)	12·5 (4–33)
Subepithelial mononuclear cell infiltrate n (%)		
Mild	14 (64)	14 (61)
Moderate	6 (27)	8 (35)
Severe	2 (9)	1 (4)
Histological HPV infection n (%)	20 (87)	21 (91)

and cytological follow-up for at least 12 months was a requirement for entry into the study. Among patients with an apparently satisfactory initial cure it was possible to identify from the histology of the pretreatment colposcopic biopsies features associated with the development of recurrent CIN This has implications both for the understanding of the mechanism of recurrence of CIN after treatment and for the routine reporting of colposcopic biopsies when these histological features might allow the identification of a group of women at high risk of recurrent disease.

All the recurrences in the present study were associated with CIN 3 at presentation, but this may partly reflect a selection bias for treatment of women with higher grades of CIN as well as the biological behaviour of high-grade CIN. Recurrence of lower-grade CIN does occur. Most of the recurrences in this study were CIN 3, but some lower-grade CIN recurrences were also found. CIN 3 lesions are generally larger than lower-grade lesions and are often associated with surrounding CIN 2 and CIN 1. There is also more than tenfold variation in the size of CIN 3 lesions (Jarmulowicz *et al.* 1989). The importance of the extent and depth of endocervical crypt involvement by CIN 3 in determining the outcome of the treatment raises the question whether recurrence of CIN results from de-novo malignant transformation of regenerated epithelium or from microscopic failure to remove all disease. The involvement of endocervical crypts by CIN is a potential cause of treatment failure as nests of dysplastic epithelium deep in the cervical stroma can regrow if only the surface epithelium has been removed. A study of cone biopsy specimens revealed that involvement can extend to a maximum depth of 7·83 mm, although in 99·7% of women with CIN 3 the depth was less than 3·8 mm (Anderson & Hartley 1980). This provides the basis for current recommendations that treatment must remove tissue to a depth of at least 5 mm. In the present study crypt involvement with CIN 3 was invariably associated with recurrence, even if this did not reach to the maximum depth of the biopsy and if treatment had extended beyond this depth and complete excision was believed to have been obtained. This suggests that either the biopsy does not always reflect the full depth and extent of CIN 3 as a consequence of sampling error, or that the depth and extent on biopsy may be an indicator of some other aspect of the aggressive potential of the disease. The limited histological sampling provided by colposcopically directed biopsy has already been identified as a mechanism for inappropriately selecting women with invasive disease for local destructive treatment (Anderson 1985).

The finding of recurrence, after apparent

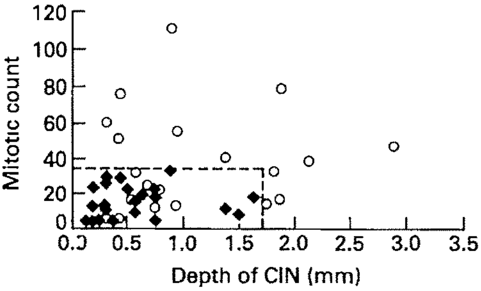

Fig. 1. Plot of mitotic count and maximum depth of crypt involvement for recurring and non-recurring CIN 3. The pecked lines exclude 59% of recurring cases.

complete histological removal of CIN 3 by cone biopsy, might indicate a field effect beyond the diagnostic histological change. The failure to remove all disease at the time of treatment remains a likely explanation of the recurrence of disease in many patients with more extensive and deep CIN 3. The use of laser cone biopsy or of loop diathermy to resect the disease and obtain a larger specimen for histological examination rather than laser vaporization after only a punch biopsy diagnosis appears advisable in those patients with extensive and deep CIN 3 on colposcopic biopsy. The use of other techniques to sample the extent of disease in the endocervix, such as blind biopsy of the base of the cone biopsy site, endocervical curettage or micro-hysteroscopy, can also help to define the full extent of CIN 3 in this group, improve the adequacy of treatment, and identify women at very high risk of recurrence. The recognition of such a group may also help to reduce the risk of the failure of laser therapy resulting in the development of invasive cancer.

The other important difference between the recurrent and non-recurrent groups was in the mitotic count: the mean metaphase mitotic count in the recurrent group was twice that of the controls and a mitotic count greater than 35/10 h.p.f. was found only in cases of recurrence. The problems of using 'high-power fields' as a unit of measurement and the sixfold variation in size of these fields have been identified by Sadler and Coghill (1989). In the present study a standard high-power field on a single microscope and measuring 1·02 mm^2 was used and sections were cut at a standard thickness using disposable microtome blades to minimize variation in section thickness. The calibration of any microscope for size of field is required before using these counts in other circumstances Increased mitotic activity and the presence of abnormal mitoses are features of CIN (Ireland & Monaghan 1985; Jenkins *et al.* 1986). High mitotic count may reflect higher proliferative activity which may be associated with more aggressive biological behaviour It has been shown to be an independent variable for the prognosis of non-Hodgkin's lymphoma (Akerman *et al.* 1987) and issued as a determinant of biological behaviour in smooth-muscle tumours (Enzinger & Weiss 1988).

The prevalence of HPV infection by histology and by common antigen staining was similar to that reported in previous studies (Jenkins *et al.* 1987, Dyson *et al.* 1984).

The local cellular response at the time of initial presentation, whether judged by the grade of mononuclear cell infiltration or by the virtual absence of S100 positive Langerhans' cells, was similar to the two groups. The Langerhans' cells have an antigen-presenting role and their paucity is in agreement with previous studies (Tay *et al.* 1987a; Hawthorn *et al* 1988) which have also shown a reduction in T lymphocytes and natural killer cells (Tay *et al.* 1987b, c). The regression of cutaneous HPV-induced lesions is associated with increased infiltration by these cells (Tagami *et al.* 1980; Arba *et al* 1986). The failure to find any overall difference in mononuclear and antigen-presenting cell populations suggests that the local immune response may not play an important part in determining the recurrence of most cases of CIN 3. However, the one patient who suffered a recurrence within 3 months of a cone biopsy had a concurrent lymphoma with possible associated systemic immunoparesis. It is well known that immunosuppression is associated with an increased risk of squamous neoplasia in the female lower genital tract (Schneider *et al.* 1983; Alloub *et al.* 1989).

In this study all patients with a depth of involvement >1·7 mm or a mitotic count above 35/10 h.p.f. had a recurrence, and 13 of 22 (59%) of recurrences were identified by these features. Care is needed in extrapolating the findings of a small case-control study to the general population of women undergoing treatment for all grades of CIN, and the figures quoted can be regarded only as a guide. However, the findings do suggest that histological features of extensive and deep crypt involvement on colposcopic biopsy, or high mitotic activity can identify a group of women with CIN 3 at high risk of recurrence. They may well require more extensive excision biopsy and careful follow-up. Attention has already been drawn to the problem of failure of laser treatment and the development of invasive cancer following laser vaporization (Cullimore *et al.* 1989). Reduction in the rate of recurrence of CIN 3 may well reduce the risk of development of invasive disease A larger, longitudinal study is needed to assess further the predictive abilities of histology in the selection of patients with CIN for alternative treatment and follow-up schedules.

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Discriminant analysis of urethral pressure profilometry data for the diagnosis of genuine stress incontinence

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Summary. Urethral pressure profilometry (UPP) has been advocated for the diagnosis of genuine stress incontinence (GSI) but no published data exist to define clearly the criteria of measurement that should be used. The aim of this study was to examine the value of UPP in the diagnosis of GSI. Data from 102 urodynamically normal women and 70 women with GSI were compared. Thirty UPP variables from the resting and stress profiles were examined. The urodynamic diagnosis was made on the basis of a pad test, uroflowmetry and videocystourethrography. Each UPP variable was examined singly and thereafter all the measurements were examined by discriminate analysis. The single most discriminatory UPP variable was 'area under the stress profile' but the overlap between normal and GSI patients was too great to allow the test to be used diagnostically. Discriminate analysis resulted in correct classification in 78% of cases. On the basis of these results, UPP is not an accurate test for the diagnosis of GSI.

The most common cause of female urinary incontinence is genuine stress incontinence (GSI). This is essentially urethral sphincter incompetence and is defined by the International Continence Society as 'involuntary loss of urine when the intravesical pressure exceeds the maximum urethral pressure but in the absence of detrusor activity' (Bates *et al.* 1976).

Urinary symptoms are common, and symptom complexes do not permit accurate prediction of the underlying pathology (Cardozo & Stanton 1980; Jarvis *et al.* 1980; Shepherd *et al.* 1982). Consequently urodynamic tests are often necessary for diagnosis.

Videocystourethrography (VCU) (Bates *et al.* 1970) is generally regarded as the best urodynamic test for the diagnosis of most common urological conditions. Unfortunately this requires radiological screening facilities which are expensive to install and maintain. For this reason cheaper urodynamic systems have been tried with varying degrees of success.

By the definition which follows from Enhorning's principle (1961), GSI occurs when the pressure in the bladder exceeds the maximum pressure in the urethra. Therefore, intuitively, it should be possible to test for sphincter competence by analysis of pressures in the lower urinary tract. The early techniques of Brown & Wickham (1969) utilized a fluid-filled perfusion system for measuring pressures at different points along the urethra whilst simultaneously measuring bladder pressure. This produced the urethral pressure profile (UPP) which yielded information about the urethra at rest Unfortunately the 'rise' time of the system was not rapid enough to cope with the pressure changes

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that take place during a cough. For this reason and because the reproducibility of these methods is not very satisfactory most urodynamicists now use the 'solid-state' systems.

The use of solid-state microtransducers mounted on a catheter was first popularized by Asmussen & Ulmsten (1975). Urethral pressure profiles obtained by this method are reliable and reproducible and, because of their rapid response time, can measure pressure changes during a cough and so are able to record a stress profile.

This latter technique is now freely available and because it is 'user friendly' has gained widespread popularity. It is possible to measure several different UPP variables at rest and under stress. However, no published data exist which clearly define the UPP measurement characteristics that can be used for the diagnosis of GSI.

Recently, Shepherd *et al.*, (1985) suggested that the maximum urethral pressure at rest could be used to diagnose GSI. However, 11 years earlier Edwards & Malvern (1974) had shown that the amplitude of the profile was only diagnostic in 66% Arguably the cough or stress profile is more relevant when the integrity of the urethral sphincter is being tested. As this can be affected by the magnitude of the coughs, it has been suggested that the ratio of the pressure transmission of the cough impulse between the urethra and bladder should be analysed. Farghaly *et al* (1985) suggested that this is a useful measure for the diagnosis of GSI, but again, an earlier paper had reported to the contrary (Bunne & Obrink 1978). Previous studies have been limited to small numbers of women (except Edwards & Malvern 1974) and have concentrated on only one urethral pressure variable at a time.

In the present study, 172 women have been assessed. The VCU, pad test and uroflowmetry findings were used to provide the urodynamic diagnosis and served as the basis for the analysis of the UPP data. Each variable was scrutinized individually and then discriminate analysis was employed to look at all 30 variables to determine which and how many of these were necessary to obtain the greatest diagnostic accuracy.

Patients and methods

The incontinent group comprised women who were referred to the urodynamic clinic with the complaint of stress incontinence and in whom urodynamic studies confirmed the diagnosis of GSI. Recruitment also took place from the Dulwich Menopause Clinic where patients had presented complaining of climacteric symptoms. These symptoms were predominantly vasomotor in nature but because they also complained of frequency and urgency of micturition (no incontinence), they were referred for urodynamic assessment. Only women who were found to be urodynamically normal and continent on pad testing were recruited for this study. None of these women had undergone bladder neck surgery for incontinence or prolapse but about a third had previously had a hysterectomy for other benign gynaecological conditions.

The women provided full gynaecological and urological history and had a general gynaecological examination to exclude significant prolapse or any other gynaecological abnormality. Urine samples were examined microscopically and cultured to exclude a urinary tract infection. Urodynamic assessment consisted of a simple pad test (Versi & Cardozo 1986), uroflowmetry and VCU (Bates *et al.* 1970).

The UPP technique was the same as that reported by Hilton & Stanton (1983) using a Gaeltec 7 French Catheter with two solid-state depressed transducers mounted 6 cm apart. Recordings were taken in the supine position with 250 ml of physiological saline in the bladder. The orientation of the transducers was lateral (9 o'clock).

Initially the catheter was passed through the urethra such that both transducers were in the bladder. The catheter was then withdrawn at a speed of 2·5 mm/ps and as the proximal transducer passed through the urethra, the resting profile was recorded (Fig. 1a). The same procedure was carried out with the woman coughing repeatedly to obtain a stress profile. Figure 1b depicts the recordings from the urethral and bladder transducers with the middle trace being the electronic subtraction. The stress profile (Fig. 1c) is just the subtraction trace with the dotted line outlining the profile.

Recordings of resting (Fig. 1a) and stress (Fig. 1c) profiles were regarded as satisfactory if two consecutive profiles were the same. Measurements were also taken with the urethral sensor at the point of maximum urethral pressure. For this the woman had to lie perfectly still for 2–3 min while a pressure trace was obtained, then she was asked to cough once and the response was

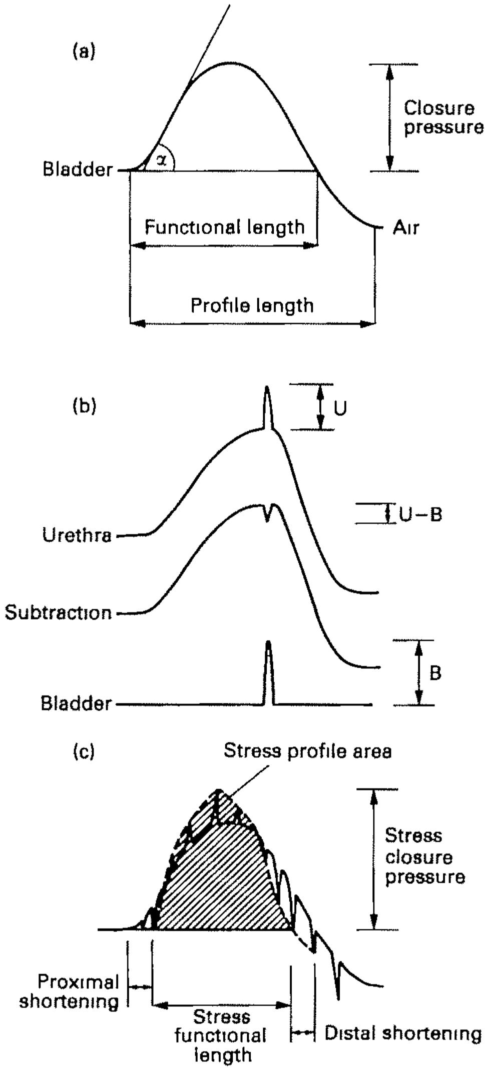

Fig. 1. (a) The resting urethral pressure profile. (b) Urethral and bladder traces of the UPP. The middle trace is an electronic subtraction of the two. A single cough is represented and results in a notch in the subtraction trace as the cough impulse to the urethra is less than that to the bladder. (c) Subtraction trace depicting the stress urethral pressure profile which is outlined by the dotted line.

measured. Finally she was asked to cough six times and the response to this was also recorded (Fig. 2).

Measurement and analysis

The variables of the resting and stress pressure profiles were measured as depicted in Fig. 1a and 1c respectively. The Hewlett-Packard digitizer was programmed to enable measurement of the areas under the resting and stress profiles. To estimate the rate of change of pressure in the proximal urethra, a regression line was fitted to the digitized points on the curve, proximal to the peak point. The gradient of this line was then used in the analysis (see Fig. 1a)

The response to a single cough and to six coughs (Fig. 2) was measured on the subtraction trace by noting the instantaneous minimum pressure during the cough, the sustained urethral closure pressure following the cough(s) and the recovery time to the maximum urethral pressure (MUP). The vascular pulsations (seen as small oscillations on the trace at the MUP) and the variations in the MUP were also measured.

Transmission pressure ratios (TPR) are a measure of the differential transmission of the cough impulse to the urethra and bladder and were calculated as shown in Fig. 3. For every woman the TPR of every cough in the stress profile was calculated. The functional urethral length was then divided into four equal lengths and the mean TPR computed for each quartile for each woman. The maximum TPR (TPR-max.) was noted for each woman as was the point on the urethra where it occurred (TPR-mode) as shown in Fig. 4.

All the information was stored on the London University mainframe computer, and the Statistical Package for Social Sciences (SPSS-X) was used for the analysis. The Kolmogorov–Smirnov test was used to test for the normality of each UPP variable.

Kappa is a statistic that can be used to measure the agreement between tests (Cohen 1968; Landis & Koch 1977; Versi *et al.* 1986). Kappa values of zero imply no agreement and a value of 1 would imply a perfect agreement. In this instance the comparison was between the VCU and the UPP findings.

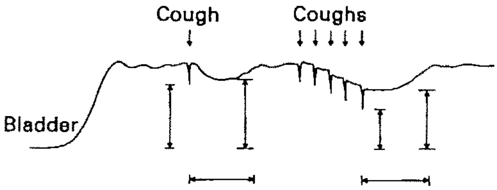

Fig. 2. Urethral pressure profile obtained with the catheter positioned so that the urethral sensor is at the point of maximum urethral pressure The effects of a single and multiple coughs are represented

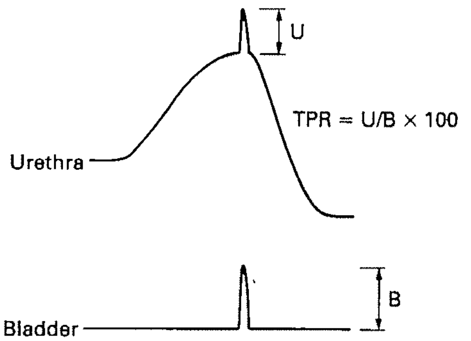

Fig. 3. Transmission pressure ratios which are calculated by dividing the magnitude of the cough impulse to the urethra by that to the bladder and multiplying the result by 100

For every UPP variable there was considerable overlap in values between continent urodynamically normal women and those with GSI. To find the cut-off point along that variable which allowed the greatest discrimination, an iterative method was used. By sequentially moving the cut-off point from the lowest to the highest value, a series of 2 × 2 tables was generated. From these 2 × 2 tables the sensitivities, specificities, false-positives, false-negatives and kappa values were calculated. Thus for every variable there was one cut-off point that generated the greatest kappa and so minimized the false-negatives and false-positives. By carrying out this process for all the 30 variables listed in Table 1, a maximum kappa value was obtained for each. The variable with the greatest maximum kappa was then reasoned to be the most discriminating single parameter.

Discriminant analysis was used to achieve a greater separation between women who were continent and those with GSI by examining all the UPP variables at once. Though a complicated technique, it is easy to use with the SPSS system, and a clear simple explanation is provided in the SPSS-X statistical manual; a more thorough explanation can be found in a treatise by Klecka (1987). The VCU findings were used to define the groups (GSI or normal) and the UPP variables were then treated as independent predictor variables. A function was created as follows:

$F = C + aA + bB + cC + dD + eE + \ldots + nN.$

where C is a constant, a is the coefficient of the variable A, and b is the coefficient of the variable B, etc. In this analysis, A, B, C, etc. were the UPP variables. As the predictor variables have to be independent, the 'total area under the resting profile' and 'total area under the stress profile' were excluded from the discriminant analysis as they were represented by their component parts (Table 1). The computation initially solved for all 28 coefficients (30 −2 = 28) which are called the standardized canonical discriminant function coefficients. Then F was computed to yield the discriminant score for every woman. This score was then used to classify that woman as either normal or GSI.

In practice, the analysis need not necessarily use all the available variables but can select only those that will result in the best separation between the defined groups. This is done by a stepwise selection procedure whereby variables are accepted or rejected until only the essential ones remain. There are many different techniques available for this stepwise selection procedure and all five available on the SPSS-X were tried.

Wherever possible, the terms used have been in accordance with the recommendations of the standardization committee of the International Continence Society (Bates *et al.* 1976).

Results

Table 2 displays the results of uroflowmetry and cystometry for the group of women with GSI and

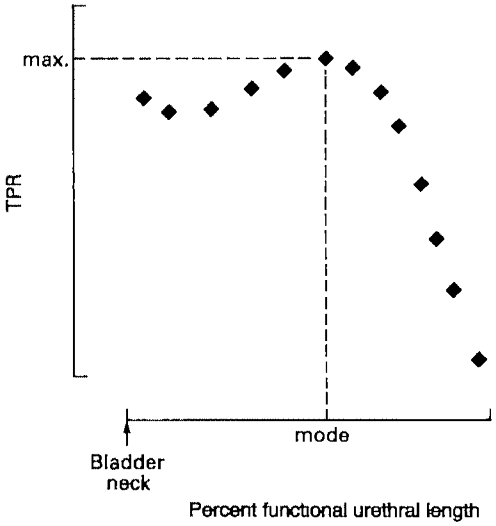

Fig. 4. Distribution of the transmission pressure ratios (TPR) along the functional length of the urethra. For any given patient there will be one cough that results in the greatest TPR, the TPR-max, and the point on the urethra where it occurs is denoted as TPR-mode

Table 1. Urethral pressure profile (UPP) in women with genuine stress incontinence (GSI)

		GSI		Normal			
UPP variable	Distribution	Mean	SD	Mean	SD	Test	Max kappa
Age of women (years)		51·5	(7·8)	49·7	(6·8)	NS	—
Resting profile							
Total area (mm cm water)	Normal	157·2	(63·5)	218·9	(80·4)	***	0·38
Area to peak (mm cm water)	Normal	73·4	(41·6)	92·7	(56·4)	*	0·22
Area after peak (mm. cm water)	Skewed @	84·3	(42·2)	127·6	(57·4)	***	0·33
Length to peak (mm)	Normal	12·9	(4·1)	13·3	(4·6)	NS	0·16
Functional urethral length (mm)	Normal	26·1	(4·0)	29·1	(4.8)	***	0·21
Total profile length (mm)	Normal	31·1	(5·5)	34·2	(5·6)	***	0·18
Maximum urethral closure pressure (cm water)	Normal	41·2	(15·2)	52·3	(17·9)	***	0·31
Maximum urethral pressure (cm water)	Normal	53·2	(18·3)	63·9	(18·7)	***	0·28
Pressure gradient in proximal urethra (degrees)	Normal @	43·8	(14·6)	48·0	(12·8)	*	0·25
Stress profile							
Total area (mm cm water)	Skewed	49·3	(54·4)	112·5	(63·0)	***	0·41
Area to peak (mm cm water)	Skewed	30·6	(71·2)	54·3	(40·2)	*	0·38
Area after peak (mm. cm water)	Skewed @	32·7	(68·8)	58·1	(40·2)	**	0·39
Length to peak (mm)	Skewed	6·4	(5·5)	10·9	(4·7)	***	0·23
Functional urethral length (mm)	Skewed @	10·8	(8·1)	19·5	(5·7)	***	0·33
Maximum urethral closure pressure (cm water)	Skewed	25·4	(40·8)	42·2	(24·6)	**	0·27
Pressure gradient in proximal urethra (degrees)	Skewed @	28·9	(24·3)	44·2	(18·5)	***	0·30
Transmission pressure ratios (TPR)							
First quartile	Normal @	88·5	(13·4)	84·8	(18·1)	NS	0·03
Second quartile	Normal	82·7	(20·3)	82·8	(16·4)	NS	0·10
Third quartile	Normal	68·8	(21·9)	76·5	(20·7)	*	0·21
Fourth quartile	Normal @	39·3	(28·9)	49·4	(29·1)	*	0·26
TPR-max.	Skewed	97·8	(24·0)	101·3	(17·6)	NS	0·26
TPR-mode	Skewed	27·3	(24·7)	38·7	(26·9)	**	0·28
At maximum urethral pressure (MUP)							
Amplitude of vascular pulsations (cm water)	Skewed	2·9	(3·3)	4·0	(3·5)	*	0·09
Variation in MUP (cm water)	Skewed	14·6	(13·3)	14·6	(10·1)	NS	0·00
Closure pressure to a single cough (cm water)	Skewed	23·2	(24·3)	36·7	(24·0)	***	0·29
Recovery time from single cough (s)	Normal	7·1	(5·7)	7·2	(6·8)	NS	0·00
Sustained pressure response to a single cough (cm water)	Normal @	33·2	(17·8)	41·0	(19·9)	**	0·26
Closure pressure to multiple coughs (cm water)	Skewed	7·8	(13·4)	20·4	(17·6)	***	0·31
Recovery time from multiple coughs (s)	Normal	8·7	(5·5)	9·3	(5·3)	NS	0·02
Sustained pressure response to multiple coughs (cm water)	Normal	22·3	(17·7)	33·3	(19·2)	***	0·33

* $P<0·05$; ** $P<0·01$; *** $P<0·001$.

NS, Not statistically significant; @ variable used in stepwise selection.

Table 2. Uroflowmetry and cystometry data in women with genuine stress incontinence (GSI) and a group of urodynamically normal women

Variable	GSI		Normal	
Peak flow rate (ml/s)	27·1	(12·4)	26·4	(12·1)
Bladder capacity (ml)	482	(422)	499	(520)
Detrusor pressure rise on filling (cm water)	5·4	(5·5)	6·4	(8·6)
Maximum voiding pressure (cm water)	33	(17)	34	(19)

Mean (SD) values are shown. There was no statistically significant difference between the two groups for any of the variables (Mann–Witney *U*-test).

the group of women who were urodynamically normal. As there was no significant difference between the means of these variables in the two groups, the normal group was subsequently treated as a control group for the analysis of the UPP data.

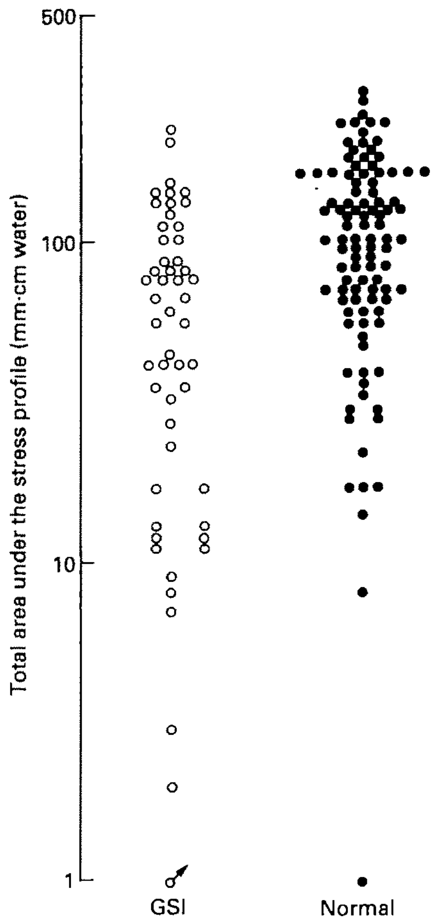

Fig. 5. Distribution of the values for total area under the stress profile (on a semi-log scale) in women who were continent (●) and women with genuine stress incontinence (○) (note ♂ denotes 19 values).

Table 1 shows the mean (SD) values for all the variables measured for the 172 women in this study. A comparison of the averages for each variable between the two groups was carried out using the *t*-test when the data were normally distributed and the Mann–Whitney *U*-test when they were not. There was no statistically significant difference in age between the two groups. However, 23 out of 30 variables had an average that was statistically significantly different between normal and GSI groups. In some there was a high level of significance.

Kappa analysis revealed that the most discriminatory single variable was 'area under the stress profile'. The actual values for each women are plotted in Fig. 5 which has a log scale. Even this variable, which had the best separation, has an overlap that is so great that any cut-off point imposed on this distribution would result in an excessive number of false-negatives and false-positives.

In the discriminant analysis, when all the variables were used in the calculation, 135 (78%) of the women were correctly classified (Table 3). Irrespective of the separation technique employed, when a stepwise selection method was used, nine variables were selected and these are indicated in Table 1. With the stepwise method, 128 (74%) of the women were correctly

Table 3. Discriminant analysis of the urethral pressure profile (UPP) measurements in women with genuine stress incontinence (GSI) Efficacy data

	UPP findings		
VCU diagnosis	GSI	Normal	Total
GSI	54 (77%)	16 (23%)	70
Normal	21 (21%)	81 (79%)	102
Totals	75	97	172

assigned to the normal or GSI group on the basis of the nine chosen UPP variables. Therefore reducing the number of variables in the calculation from 28 to 9 resulted in only seven more women being misdiagnosed.

Figure 6 shows the comparison between UPP and VCU data using discriminant analysis and employing all the variables to obtain the greatest possible separation. With the VCU result acting as the 'gold standard', UPP data yield a sensitivity of 77·1% and a specificity of 79.4%, the false-positive and false-negative rates being 20.6% and 22·9% respectively (Table 3).

From Fig. 6 it is possible to construct a probability plot. This yields the likelihood of GSI given the discriminant score derived from a UPP test (Fig. 7). Such a plot is useful as it allows the investigator to assess the accuracy of the test result and so determine equivocal cases.

Discussion

The aim of this study was to assess the use of UPP measurement for the diagnosis of GSI. For this purpose the VCU findings are assumed to have provided the correct diagnosis and so have acted as the 'gold standard' against which the UPP data have been measured.

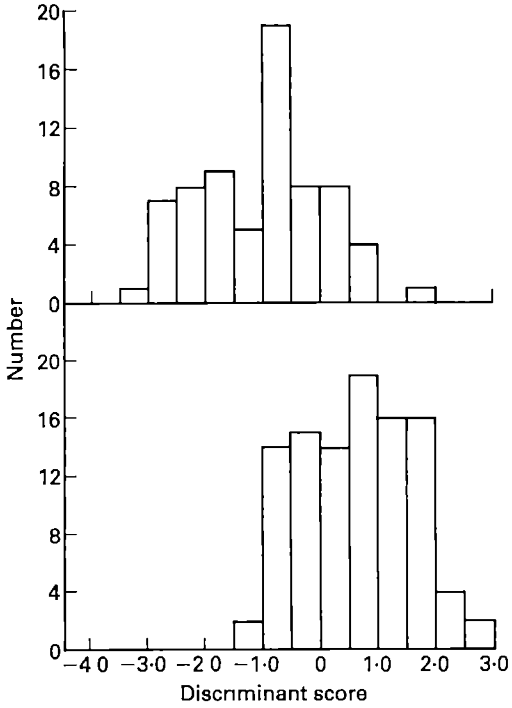

Fig. 6. Histograms of the distributions of the discriminant scores for patients with GSI (above) and normal (below). Note the still considerable overlap.

The most discriminating single variable was 'area under the stress profile' but even here the overlap between normal and GSI was so great as to make this variable unacceptable for diagnostic purposes (Fig. 5).

With discriminant analysis, employing all the variables, only 78% of the women were correctly classified. This is a rather poor result when it is remembered that a 50% correct classification could be achieved merely by chance. The stepwise selection procedure using only nine variables resulted in a reduction in accuracy to 74% and did not really simplify the situation.

Measurements of UPP are reproducible with regard to the resting profile (Hilton 1983) and so it is regarded as a reliable technique. On theoretical grounds, the technique should be useful for the diagnosis of GSI but the data presented here suggest that this is not the case in practice. It is not clear why there should be this discrepancy.

The correct way to measure the pressure in a collapsed tube (like the urethra) has not been satisfactorily resolved (Griffiths 1985). The catheter employed should be thin and flexible. The catheter used in the present study was soft, being made of sialastic and only 7 French gauge.

Our microtip transducer technique may be prone to artefact during generation of the stress profile due to catheter movement on coughing. However, this can be minimized by ensuring that the woman does not move during the cough and

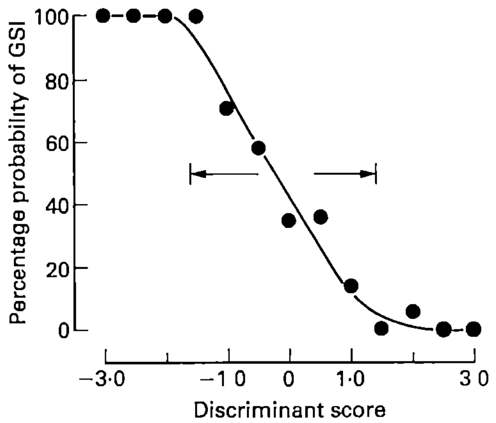

Fig. 7. The curve is generated from the data presented in Fig. 6. For any given discriminant score, the probability of GSI can be read from this curve The equivocal range has been indicated with bars.

that the catheter withdrawal device is positioned at the same height as the external urethral meatus. Nonetheless, it is for this reason that the stress profile is generally thought to be less reproducible than the resting profile.

Another source of artefact may be introduced when the urethra is significantly curved but this problem can be minimized by using a lateral orientation (Anderson *et al.* 1983) as was done in our study. It could be argued that the orientation employed was suboptimal but the lateral position used in this study has been shown to exhibit the lowest coefficient of variation (Hilton 1983). Hosker *et al.* (1984) have argued that an anterior orientation is more discriminatory but their data were preliminary, consisting of only 20 patients per group, and they have not published any reproducibility data to substantiate their claim. Regardless of what the optimal technique might be, what is germane to this paper is that the equipment and the technique used in this study are the same as those used in many centres worldwide for the routine diagnosis of GSI. Thus the main thrust of this paper is to highlight the shortcomings of an accepted and widely practised urodynamic technique.

Many of the UPP variables measured have averages (means or medians) that are significantly different between normal women and those with GSI (Table 1), and this fact has provided impetus for the use of UPP as a diagnostic tool. What has not been appreciated is that there is a large overlap in the measurements found in these two groups (Fig. 5) and so these data cannot be used to discriminate on the basis of any single UPP variable. Even when all the variables are combined to formulate criteria for the diagnosis of GSI (discriminant analysis), though the separation is better, the overlap is still too great (Fig. 6).

Other authors have stated that UPP data can be used for the diagnosis of GSI (Shepherd *et al.* 1985; Farghaly *et al.* 1985), but there is little difference between their results and those presented here. However, there is a difference in interpretation and this is because these authors have not subjected their data to the stringent analysis presented in this paper. As far as it is possible from their published data, re-analysis leads to a similar conclusion to that presented here.

Many of the variables measured were not normally distributed and so on strictly theoretical grounds discriminant analysis should not be used here. In practice, however, many authorities on the subject (Klecka 1987) have stated that the technique is rather robust and when a large number of cases are being used in the analysis (as was the case here), the assumption of normality is not so essential (Lachenbruch 1975).

It could be argued that women from a menopause clinic were not normal in that they were suffering from climacteric symptoms. Most sampling methods in clinical research are subject to some selection bias but the women in this study were comparable for age, uroflowmetry and cystometry variables (Table 2) and there was no other obvious source for bias. For the purposes of this study if VCU data are accepted as reliable, the problem of normality is obviated as it is defined on the basis of the VCU findings. Videocystourethrography may not be the perfect test but it is the best one available and so should be held as the 'gold standard'

No single UPP variable can be used for the diagnosis of GSI and so this method is useless in the clinical setting The reason for this is the large number of false-positives and false-negatives generated by this test. Both types of errors are undesirable but false-positive errors have greater consequences within the clinical context in that they may result in unnecessary surgery. Nonetheless, for the test to be more useful, both the false-positive and the false-negative rates should be minimized. The kappa statistic serves as a measure of this goal.

However, the data from discriminant analysis are of some use. By examining the graph in Fig. 7 it can be seen that a woman with a given discriminant score has a calculable probability of having GSI. On this basis it may be possible to determine clinical management. Patients with an equivocal probability (those falling between the bars—unfortunately a fair number) could be referred for VCU studies.

On the practical front, it would be difficult for a urodynamicist to measure all 30 UPP variables in every woman and then to calculate laboriously the discriminant score by using the previously calculated standardized canonical discriminant function coefficients. Fortunately many microtip catheter systems are now sold with a microprocessor and the package is relatively cheap. It would be possible to write the appropriate software to allow instant calculation of the UPP results. Thus a UPP examination could be concluded with one of three results: GSI, normal, or refer for further studies.

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The use of mifepristone (RU 486) for cervical preparation in first trimester pregnancy termination by vacuum aspiration

WORLD HEALTH ORGANIZATION

Task Force on Post-ovulatory Methods for Fertility Regulation Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland

Summary. Animal and clinical evidence suggests that the antiprogestin mifepristone may be of potential use for cervical preparation before surgical termination of pregnancy. A double-blind, multicentre study was undertaken of 230 primigravid women with 10–12 weeks amenorrhoea who were randomly assigned to groups given 0 (placebo), 25, 50 or 100 mg mifepristone twice at 24 and 12 h before vacuum aspiration. In mifepristone-treated women the cervix was on average between 0.9 and 1.2 mm more dilated at operation, but the effect was not dose related. High resistance during further mechanical stretching tended to be encountered more often and at a smaller cervical diameter in the placebo group than in the women given mifepristone, but these differences were not statistically significant. In contrast, the ease of dilatation assessed subjectively by the operating surgeons was not only improved by the antiprogestin, but was also dose related. Mifepristone therapy was not associated with any side-effects and only two of the women from the highest dose group experienced preoperative vaginal bleeding. Peroperative blood loss, post-operative complications, the duration of post-operative bleeding and the interval to the first period were similar in the four treatment groups.

It is well known that the frequency of complications associated with surgical termination of pregnancy rises as gestation advances (see Frank 1985 for review). The need for greater mechanical dilatation of the cervix carries an increased risk of cervical laceration and uterine perforation and may have an adverse long-term effect on subsequent fertility. In addition, complica-

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tions such as haemorrhage and incomplete evacuation of the products of conception may arise as a result of insufficient or difficult dilatation. For these reasons a variety of procedures has been investigated with the aim of developing a simple, safe, and less traumatic method for preparing the cervix before dilatation and suction or mechanical curettage, particularly when performed in more advanced first trimester pregnancies. The two main types of pretreatment currently used are the administration of prostaglandins (PGs) (see Lauersen 1986 for review) and the introduction of a cervical dilator such as a laminaria tent or Lamicel, a synthetic hydrophilic polymer impregnated with magnesium sulphate (Helm *et al.* 1988).

In pregnant guinea-pigs, the antiprogestational steroid mifepristone (RU 486) causes marked cervical dilatation and softening, apparently without stimulating uterine contractions (Elger *et al.* 1987). Reduced stiffness (Rådestad *et al.* 1988) and increased dilatation of the cervix (Durlot *et al.* 1988) have also been reported recently following mifepristone treatment during the first trimester of human pregnancy. In both studies the antiprogestin was given in a daily dose of 200 mg for either 24 (Rådestad *et al.* 1988) or 48 h (Durlot *et al.* 1988) before surgical termination of pregnancy.

The present randomized, double-blind, multicentre study was undertaken to determine whether the effect of mifepristone on the cervix was dose dependent. To minimize the risk of preoperative uterine bleeding, which was experienced by 18 (62%) of the 29 women treated by Durlot *et al* (1988) as opposed to only four (20%) out of the 20 subjects treated by Rådestad *et al.* (1988), mifepristone was given for 24 h.

Subjects and methods

Ethical approval for the study was obtained from WHO's Secretariat Committee for Research into Human Subjects and from the corresponding ethics committees in the six participating centres.

The women studied were primigravidae, aged 18–35 years, for whom legal abortion had been agreed before recruitment to the study. All gave their informed consent after the study had been explained, including their right to withdraw from the trial at any time without prejudice to their further medical care. Criteria for inclusion were a normal general and gynaecological history and examination, amenorrhoea of not less than 70 days and not more than 84 days (as calculated from the first day of the last menstrual period) on the day mifepristone treatment was given (i.e. the day before vacuum aspiration), and ultrasonographic confirmation that the pregnancy was intrauterine, that fetal heart activity was present, and that the size of the gestational sac was appropriate. Women with a history of previous cervical surgery or dilatation as well as those with threatened miscarriage were not recruited. Also excluded were women who intended to start hormonal or intrauterine contraception before their first menstruation after the abortion.

The study involved a randomized, double-blind comparison between four treatment regimens: 0 (placebo), 25, 50 or 100 mg mifepristone given twice at 24 and 12 h before vacuum aspiration. These four treatment groups are henceforth referred to as the placebo, 25 mg, 50 mg and 100 mg groups, respectively. The total sample size was fixed at 60 per group. Under the assumption that cervical dilatation has a standard deviation of 1·8 mm (WHO Task Force on Prostaglandins for Fertility Regulation 1986), this would permit detection of 1·2 mm differences in dilatation (one-sided test, 1% significance level, 90% power); that is, about half that observed with a PG analogue such as 15-methyl-$PGF_{2\alpha}$ methyl ester (WHO Task Force on Prostaglandins for Fertility Regulation 1981). Each participating centre was therefore requested to recruit 40 women and provided with the same number of coded treatment courses, dispensed by the Galenic Department of Roussel-Uclaf (Paris, France) in accordance with the computer-generated random treatment tables (one for each centre) provided by WHO Headquarters.

All the women had a blood sample taken for haemoglobin measurement on admission and were kept under clinical observation from the start of treatment until at least 6 h after vacuum aspiration. Immediately before the first tablet and at 6 h intervals thereafter until the aspiration procedure, blood pressure and pulse rate were measured and any side-effects or vaginal bleeding were recorded.

Each centre was free to perform vacuum aspiration after its usual practice but was requested to carry out all procedures using the same type of anaesthesia and instruments. To minimize between-observer variation, most, if not all, aspirations were done by the same surgeon except in one centre where unforeseen circumstances necessitated a change of surgeon about halfway through the study.

At the time of vacuum aspiration the operating surgeon inspected the cervical os for the presence of uterine bleeding and, by passing sequentially Hegar dilators of increasing size, determined the degree of cervical dilatation present, the amount of further dilatation required to permit passage of the chosen size suction catheter, the ease of dilatation and, where applicable, the degree of dilatation at which 'high resistance' had to be overcome. The degree of cervical dilatation present was defined as the largest Hegar dilator that could be passed through the internal cervical os without encountering resistance. The ease of dilatation was judged subjectively on a 5-point scale—very easy, easier than normal, normal, more difficult than normal and very difficult—while 'high resistance' was defined as the point when during dilatation the dilator tended to be expelled spontaneously back into the vagina and increased traction on the vulsellum attached to the cervix and firmer pressure on the dilator were required to achieve further dilatation. Any complications encountered during the aspiration were recorded and the amount of blood and fluid loss was measured after sieving the contents of the collection jar to remove fetal, placental and decidual tissues.

On discharge from hospital a blood sample was taken for haemoglobin measurement. A follow-up visit was arranged 8 weeks later when a gynaecological examination was made and the woman was questioned about possible delayed complications, the duration of vaginal bleeding and the date of onset of her menstrual period.

All data were recorded on standardized forms and analysed at WHO in Geneva. Comparisons between treatment groups and centres were made by the χ^2 test or analysis of variance, as appropriate. The paired *t*–test was used to determine the significance of changes in haemoglobin levels from pretreatment values. Findings were considered statistically significant only if they reached the 1% level.

Results

A total of 230 women was entered into the trial (one centre did not succeed in recruiting its full quota of 40 subjects), but 18 were excluded from analysis because they had some characteristic which deviated from the inclusion criteria specified in the protocol (in 11 women this was the duration of amenorrhoea). These criteria were written into a computer program so that the exclusions were made automatically, in ignorance of treatment group or outcome.

Relevant clinical characteristics of the remaining 212 subjects on admission are summarized in Table 1. In addition to the variables listed in Table 1, women in the four treatment groups were also similar in respect of uterine size as assessed by pelvic examination and in the reported occurrence of pregnancy-related complaints (nausea, vomiting, dizziness, fatigue and lower abdominal discomfort). The frequency of these complaints remained unchanged following the start of treatment and only two women in the 100 mg group experienced vaginal bleeding (15 ml and 55 ml respectively). One woman in the placebo group withdrew from the study after taking the first tablet and continued the pregnancy.

Vacuum aspirations were done under general anaesthesia except in one centre where paracervical anaesthesia was used. Findings at operation are summarized in Tables 2 and 3.

Blood was seen at the cervical os in seven (3%) of the women, including the two with preoperative blood loss. There were significant differences in the degree of cervical dilatation present between all four treatment groups ($P<0{\cdot}005$), between the placebo group and the three mifepristone groups combined ($P<0{\cdot}001$), but not between the three mifepristone groups. There were also significant differences between centres ($P<0{\cdot}001$), but no interaction between treatment group and centre; that is, the effect of treatment did not differ between centres.

In all but eight women the cervix required further mechanical dilatation. High resistance tended to be encountered more often in the placebo group (73%) than among women given mifepristone (60% overall) but the difference was not statistically significant. Moreover, it was less common among subjects in the 25 mg group (54%) than among those who received the highest dose (65%). The degree of dilatation at which high resistance was encountered tended ($P<0{\cdot}05$) to be lower in the placebo group (7.9 SD1·6 mm) than in the three mifepristone groups (25 mg· 8.5 SD1·6 mm; 50 mg: 8.6 SD1·7 mm; 100 mg: 8.8 SD1·5 mm)

Table 1. Subject characteristics (mean, SD) on admission, by treatment group

Characteristic	Treatment group Placebo ($n = 54$)	 25 mg ($n = 48$)	 50 mg ($n = 56$)	 100 mg ($n = 54$)
Age (years)	22·1 (3·9)	20·8 (2·5)	21·2 (2·6)	21·3 (3·4)
Weight (kg)	56·5 (9·0)	57·6 (8·1)	55·4 (9·2)	54·5 (7·6)
Height (cm)	163·5 (7·6)	163·5 (5·9)	163·2 (6·7)	161·8 (6·9)
Average cycle length (days)	29·4 (2·0)	29·1 (1·7)	29·0 (1·7)	29·4 (2·0)
Duration of amenorrhoea (days)	73·9 (4·3)	74·8 (4·2)	74·7 (4·3)	74·9 (4·6)
Diameter of amniotic sac* (mm)	43·6 (11·8)	44·3 (9·1)	45·0 (9·4)	44·4 (9·1)
Haemoglobin (g/l)	126·6 (10·8)	129·0 (9·9)	127·4 (10·4)	127·6 (9·6)

*All subjects had a single amniotic sac.

although, again, there were no differences between the doses. In contrast, the ease of dilatation was not only improved by mifepristone, but was also dose related. It was described as very easy in only 10% of subjects who received the placebo, but in 17%, 22% and 35% of women, respectively, in the 25, 50 and 100 mg groups (Table 3). Neither the average time required to perform the aspiration (about 8 min) nor the median amount of blood and fluid lost (about 100 ml) differed significantly between the four treatment groups. Apart from four women with cervical laceration, no peroperative complications were encountered.

In most women the immediate post-operative period was uneventful. One woman from the placebo group who had sustained a cervical laceration and a blood (and fluid) loss of 325 ml during the aspiration was given intravenous Ringer solution and oxytocin. Haemoglobin levels on discharge from hospital were similar in the four groups, but the mean (SE) decreases from pretreatment levels tended to be greater in the three mifepristone-treated groups (25 mg: 2·2 SE 1·0 g/l, $P<0·05$; 50 mg: 2·7 SE 1·1 g/l $P<0·05$; 100 mg: 3·0 SE 1·1 g/l, $P<0·01$) than in the placebo group (1·8 SE 1·0 g/l, $P<·05$).

Among the 190 (90%) women who attended the 8-week follow-up visit, the duration of post-operative bleeding was similar in the four treatment groups with median values ranging from 5·0 to 6·5 days. There were also no differences between the four groups in the proportion of subjects who had had menses which ranged from 95 to 100%, nor in the time to return of menses (median values from 34.0 to 36.0 days). Two women were found on ultrasound examination to have become pregnant again and were readmitted for pregnancy termination.

The frequency of delayed complications was similar in the four groups. Overall, such complications occurred in 13 women, i.e. 6% of aspiration procedures, if it is assumed that the 21 women who did not attend the follow-up visit had no delayed complication. Four women (one from the placebo and three from the 25 mg group) required curettage because of incomplete abortion; in the placebo-treated subject

Table 2. Mean (SD) cervical dilatation (mm) present at aspiration by treatment group and centre

Centre	Treatment group Placebo	 25 mg	 50 mg	 100 mg	All subjects
Aberdeen	4·9 (2·1)	5·4 (2·1)	6·3 (1·7)	5·1 (2·0)	5·4 (2·0)
Greifswald	5·6 (1·4)	7·2 (2·4)	7·2 (1·7)	7·6 (1·5)	6·9 (1·9)
Hong Kong	7·6 (1·9)	7·8 (1·3)	7·6 (1·5)	7·8 (2·2)	7·7 (1·7)
Singapore	4·9 (1·2)	6·0 (0·8)	6·1 (1·3)	6·0 (1·2)	5·8 (1·2)
Stockholm	4·4 (1·3)	5·7 (1·0)	4·6 (1·3)	5·3 (1·5)	4·9 (1·3)
Szeged	5·2 (2·5)	7·4 (1·9)	6·3 (1·2)	7·4 (1·0)	6·6 (1·9)
All centres	5·4 (2·0)	6·6 (1·9)	6·3 (1·7)	6·6 (1·8)	6·2 (1·9)

For differences between treatment groups and centres see text.

Table 3. Peroperative findings by treatment group

	Treatment group			
	Placebo ($n = 53$) n (%)	25 mg ($n = 48$) n (%)	50 mg ($n = 56$) n (%)	100 mg ($n = 54$) n (%)
Vaginal bleeding present	1 (1·9)	1 (2·1)	2 (3·6)	3 (5·6)
Cervix dilated mechanically	52 (98·1)	46 (95·8)	54 (96·4)	51 (94·4)
High resistance encountered*	38 (73·1)	25 (54·3)	33 (61·1)	33 (64·7)
Ease of dilatation*†				
Very easy	5 (9.6)	8 (17·4)	12 (22·2)	18 (35·3)
Easier than normal	16 (30·8)	22 (47·8)	20 (37·0)	14 (27·5)
Normal	12 (23·1)	12 (26·1)	13 (24·1)	14 (27·5)
More difficult than normal	14 (26·9)	3 (6·5)	6 (11·1)	4 (7·8)
Very difficult	5 (9.6)	1 (2·2)	3 (5·6)	1 (2·0)
Complications	1 (1·9)	0 (0·0)	·1 (1·8)	2 (3·7)

*Percentages calculated as proportion of subjects in whom cervix was dilated further mechanically.
†Significantly different ($P<0·01$) between groups

the curettage was carried out as an emergency procedure because of associated heavy vaginal bleeding. The remaining nine women (placebo: 1; 25 mg: 2; 50 mg: 2 and 100 mg: 4) with a delayed complication were treated with antibiotics because of clinically suspected pelvic or urinary tract infection.

Discussion

This is the first report of a randomized, double-blind, multicentre dose-finding study on the use of mifepristone for cervical preparation prior to vacuum aspiration in late first trimester pregnancy.

Effective cervical preparation for dilatation and curettage in first trimester pregnancy interruption can be obtained with laminaria or similar synthetic dilators as well as with several PG analogues. However, the former requires insertion by a doctor whereas the use of PGs is commonly associated with gastrointestinal side-effects and lower abdominal pain (see Lauersen 1986 for review). Treatment with mifepristone, on the other hand, proved to be completely free of these adverse effects. Moreover, the frequency of preoperative vaginal bleeding, which could represent a potential hazard if mifepristone pretreatment were done on an out-patient basis, was low. Only two (1%) of the 158 antiprogestin-treated women noticed vaginal blood loss before the aspiration procedure. Both these women belonged to the 100 mg group ($n = 54$), giving a frequency of 4% preoperative bleeding in this group. This figure is substantially lower than the 20% (four out of 20 subjects) reported by Rådestad *et al.* (1988) who used the same treatment regimen. The reason for this difference is not clear. As might be anticipated from clinical experience with mifepristone for the termination of early pregnancy (Bygdeman & Van Look 1988), a longer pretreatment period, e.g. 48 h as used by Durlot *et al.* (1988), is associated with a higher frequency of preoperative vaginal bleeding and this could represent a hazard, particularly in situations when the bleeding is heavy and appropriately qualified personnel are not immediately available.

The degree of cervical dilatation present in placebo-treated women at the time of the evacuation procedure (5·4 mm) was similar to that observed in previous placebo-controlled, multicentre trials conducted by WHO on the cervical ripening effect of PGs (see e.g. WHO Task Force on Prostaglandins for Fertility Regulation 1981). Pretreatment with mifepristone significantly increased the degree of cervical dilatation present by an average of between 0·9 and 1·2 mm, but the effect was not dose related. A similar lack of a dose–response relation has also been observed in respect of the complete abortion rate achieved when the antiprogestin is used alone for terminating early pregnancy (see Van Look 1988 for review). The mifepristone-induced increase in cervical dilatation observed in the present trial is similar not only to the value (1·1 mm) reported by Rådestad *et al.* (1988) but also to the increase (1·2 mm) noted by Durlot *et* *al.* (1988). Since the latter authors employed a 48 h pretreatment regimen, this may suggest that the maximum effect is achieved in 24 h and that no further therapeutic benefit is gained, at least not in terms of the degree of cervical dilatation present, by extending the period of pretreatment beyond 24 h.

Using a specially designed instrument to quantify the force exerted on Hegar dilators during dilatation of the cervix, Rådestad *et al.* (1988) were able to demonstrate a lower stiffness of the cervical tissue in mifepristone-pretreated women. Likewise, in the present study, cervical stiffness was reduced by the antiprogestin as evidenced by the observation of the operating surgeons that 'high resistance' was encountered at a greater diameter of the cervix and that dilatation was easier to perform. The latter finding was dose related, suggesting that higher doses may have, in fact, a therapeutic advantage even though the use of such doses is not associated with a clinically recognizable increase in cervical diameter.

In comparison with our previous data on the use of PGs for cervical preparation, mifepristone pretreatment appears to be associated with a lesser degree of cervical dilatation and, consequently, with a higher proportion of cervices needing further dilatation. For example, cervical diameter was on average 2·3 mm greater in women pretreated for 3 h with 1 mg 15-methyl-$PGF_{2\alpha}$ methyl ester in vaginal suppository form compared with subjects receiving a placebo suppository (WHO Task Force on Prostaglandins for Fertility Regulation 1981). Likewise, among women pretreated for 3–4 h with intramuscular sulprostone (16-phenoxy-tetra-nor-PGE_2 methyl sulfonylamide), vaginal meteneprost (9-deoxo-16,16-dimethyl-9-methylene PGE_2) or vaginal gemeprost (16, 16-dimethyl-trans-Δ^2-PGE_1 methyl ester), only 71–77% required further mechanical dilatation of the cervix (WHO Task Force on Prostaglandins for Fertility Regulation 1986) compared with 94–96% of mifepristone-treated women in the present study. Randomized trials are required, however, before adequate comparisons can be made between the two approaches, not only in terms of their efficacy but also in respect of user acceptability and issues related to their provision in family planning services.

Such comparisons will also need to address the effect of the two methods on peroperative blood loss. In general, PG pretreatment tends to be associated with reduced blood loss during the evacuation procedure (Lauersen 1986); such an effect was not observed following mifepristone in the present study. Surprisingly, the antiprogestin-treated groups had a somewhat greater decrease in haemoglobin levels even though the measured peroperative blood (and fluid) loss was the same as that in the placebo group. Since mifepristone has antiglucocorticoid activity in addition to its antiprogestational activity (Baulieu 1985) and has been shown to increase plasma levels of ACTH, cortisol and arginine vasopressin (Healy *et al.* 1983) and of aldosterone (Swahn *et al.* 1989), it may be that the lower haemoglobin levels in the mifepristone groups were due to a minor degree of haemodilution.

Both the duration of post-operative vaginal bleeding and the time to return to menses were the same in placebo and mifepristone-treated women and also similar to those reported after PG priming of the cervix (WHO Task Force on Prostaglandins for Fertility Regulation 1986). The occurrence of delayed complications was also similar in the placebo and mifepristone groups, but because of the relative rarity of such complications, further studies on larger numbers of subjects need to be carried out before definite conclusions can be drawn about possible beneficial or adverse effects of mifepristone pretreatment Such studies will necessitate a collaborative effort in view of the large sample size required. For example, assuming a 0·5–1·0% rate of cervical laceration or incomplete evacuation in untreated women (Tietze & Lewit 1972; Smith *et al.* 1978), between 3700 and 7400 subjects per group (one-sided test, 5% significance level, 80% power) will be needed to demonstrate a 50% reduction in these rates resulting from mifepristone pretreatment.

The manner in which mifepristone causes cervical dilatation and softening has not been fully elucidated. Two mechanisms may be involved: a direct action of the compound on the cervix and an indirect effect resulting from the stimulation of uterine contractility. Electron microscopic study of cervical biopsies from women treated with mifepristone has demonstrated an accumulation of mast cells, dissolution of collagen fibres and an outgrowth of blood capillaries, possibly as a result of increased local PGE_2 release (Rådestad *et al.* 1990). In addition, in the pregnant rabbit, treatment with mifepristone markedly reduces the ratio of cervical α- and β-adrenoreceptors (Falkay, unpublished observations).

During normal pregnancy this ratio is high and thought to be important in maintaining the tonus of the internal cervical os. The increased uterine contractility, which can be demonstrated in a significant proportion of mifepristone-treated women 24 h after the start of therapy (Swahn & Bygdeman 1988), is likely to enhance these direct cervical effects of the compound

The present study suggests that the antiprogestin mifepristone has potential value for cervical preparation before dilatation and suction in late first trimester pregnancy termination. Whether the compound has advantages over laminaria and PGs in terms of safety, efficacy, user acceptability and service delivery awaits the results of further randomized trials.

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Raised maternal serum alpha-fetoprotein levels during pregnancy following treatment of an endodermal sinus tumour. Case report

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Case report

A previously healthy 23-year-old woman was admitted to hospital having had lower abdominal pain for eight weeks. She had an 18-cm-diameter mass arising from her pelvis that was separate from the uterus. Ultrasound scan confirmed a large ovarian cyst.

Laparotomy was performed and the tumour was removed by right salpingo-oophorectomy. There was no obvious macroscopic disease in the pelvis. There was no para-aortic lymph node enlargement and the abdominal and pelvic peritoneal surfaces were free from tumour. The histological appearance of the cyst was that of an endodermal sinus tumour which did not breach the capsule of the ovary Peritoneal washings, omental biopsies and a wedge biopsy of the left ovary were negative for tumour.

She remained well until 11 months later when she returned complaining of a tender enlarging nodule in her abdominal scar This 2-cm-diameter lesion was excised completely and was found to consist of tissue histologically the same as the original tumour. Laparoscopy detected no further disease in the pelvis or liver. She was treated with five courses of cis-platinum, vinblastine and bleomycin and her serum alpha-fetoprotein (AFP) which had become elevated to 4167 iu/ml rapidly declined to undetectable levels.

She was observed closely over the following 12 months. During this time there was no evidence of recurrence clinically or radiologically and her serum AFP levels remained undetectable.

The patient attended the antenatal clinic 4 months later when she was 13 weeks pregnant. At this visit her serum AFP was found to be elevated (Fig. 1). Affinity chromatography using a column of concanavalin A sepharose was used to characterize this AFP (Smith *et al* 1977).

The pregnancy was uneventful. Ultrasound scans of the left ovary and liver were normal as were liver function tests. Detailed scanning of the fetus at 18 weeks gestation revealed no abnormality, and fetal growth, as measured by biparietal diameter and abdominal circumference, remained on the 50th centile.

Labour began spontaneously at 42 weeks and a healthy normal baby girl weighing 3·48 kg was born vaginally. The placenta weighed 600 g and appeared healthy. The puerperium was uneventful.

Discussion

Endodermal sinus tumours (EST) of the ovary typically produce AFP which reliably indicates the presence of the tumour and its regression following treatment (Sell *et al* 1976). Conservative surgery and aggressive chemotherapy has led to improved prognosis as well as to maintained fertility in younger women (Forney 1978).

During normal pregnancy, first the yolk sac then the fetal liver and gastrointestinal tract produce AFP. Maternal serum AFP levels are used to screen for certain fetal abnormalities, particularly neural tube defects. Only two studies report levels of serum AFP during pregnancy (Duncan & Young 1980; Ward *et al.* 1982). Our report is the first to describe elevated levels of

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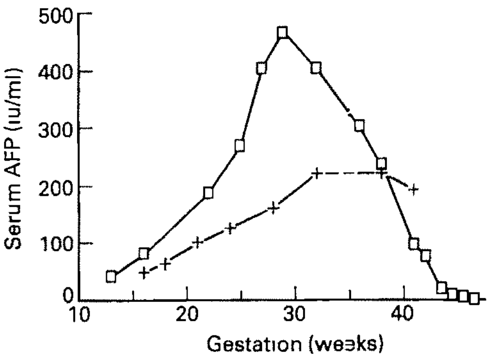

Fig. 1. Serum alpha-fetoprotein (AFP) levels in pregnancy. ☐, maternal levels; +, 98th centile values for the normal range of materni serum AFP in pregnancy.

serum AFP in pregnancy in a patient treated successfully for endodermal sinus tumour.

Our main concern was to distinguish between fetal abnormality and recurrent endodermal sinus tumour. Detailed ultrasound scanning was used to exclude major fetal anomaly while chromatographic analysis of the AFP was used to determine its source. Human AFP is heterogeneous and can be divided into various subfractions, according to different reactivities with lectins such as concanavalin A (Con A). Using affinity chromatography with concanavalin sepharose A, AFP can be separated into either a 'yolk sac' or 'liver' variant (Buamah *et al.* 1984; Chan & Miao 1986). The 'yolk sac' type of AFP contains an additional sugar, N-acetylglucosamine, which blocks the concanavalin A binding site. Thus with 'yolk sac' type AFP there is a high concanavalin A non-reactive (CNR) fraction whereas for the 'liver' type of AFP, which does not possess this sugar, the reverse is true. Endodermal sinus tumours produce 'yolk sac' type AFP (Ishiwata *et al.* 1986).

In our patient the concanavalin A non-reactive (CNR) fraction was 1·5% maximum (range 1·0–1·5%); thus the AFP subfraction was not compatible with that of yolk sac origin (Buamah *et al.* 1984). In view of this the patient was reassured that recurrence of the endodermal sinus tumour was unlikely. As detailed fetal scanning was also normal no action was taken and the pregnancy was allowed to continue.

We could confirm that the elevated serum AFP levels were not due to a recurrent AFP-producing tumour when the serum AFP levels declined at a rate appropriate to the half-life of AFP (approx. 5 days, Chan & Miao 1986) after the birth of the healthy baby. The cause for the raised serum AFP levels during this pregnancy remains unclear.

Serum AFP levels should be measured regularly during the pregnancy of women previously treated for endodermal sinus tumour. If the serum AFP is raised detailed scanning of the fetus and chromatographic separation of the AFP should be performed to exclude fetal abnormality and tumour recurrence.

Acknowledgment

We wish to thank Dr Stephen Jones of the Department of Clinical Chemistry, Queen Elizabeth Medical Centre, Birmingham, for performing the chromatographic studies.

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Virilizing ovarian serous cystadenoma. Case report

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Case report

An 80-year-old woman consulted a dermatologist because over the previous 17 years she had developed diffuse scalp hair loss (Fig. 1) and hirsutism over the chest. She was obese, with a markedly elevated free serum testosterone level of 58·5 pmol/l (normal range 1–12 pmol/l). She was referred to the gynaecological clinic. She was euthyroid and her gonadotrophin levels were in the postmenopausal range (Table 1).

A pelvic ultrasound scan revealed a left ovarian cyst with no solid areas. No adrenal enlargement was detected by a CT scan. Her chest X-ray, haemoglobin level and serum electrolyte values were normal.

Laparotomy was performed through a midline incision. There was a left ovarian cyst with an intact capsule, approximately 10 cm in diameter. There was no ascites, the uterus was atrophic and the right ovary looked normal, as did the omentum, gut, stomach, liver and diaphragm. A total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. The patient was well enough to leave hospital 5 days later. Her serum testosterone level had returned to normal (6·9 pmol/l) 2 months later, but she had not regained her scalp hair at 4 months.

The left ovarian tumour was a benign serous cystadenoma with a thin layer of luteinized cells in the cyst wall (Fig. 2). The appearances were not those of an arrhenoblastoma; rather the luteinized stromal cells appeared to be the likely source of normal hormone production. The endometrium was inactive.

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Comment

Ovarian tumours with a functioning stroma have been widely reported, but most of them secrete oestrogen. The patients are usually postmenopausal, but it is difficult to establish oestrogen production by a tumour in premenopausal women with a normal contralateral ovary. In a recent review, Scully (1987) identified only 42 ovarian tumours with a virilizing stroma, 19 of them were described in pregnant women. Such virilizing tumours are predominantly malignant and when benign often mucinous.

Virilizing ovarian serous cystadenoma is a very rare condition. An extensive literature search yielded one previous report in pregnancy (Fayez *et al.* 1974).

Our patient had a benign serous cystadenoma

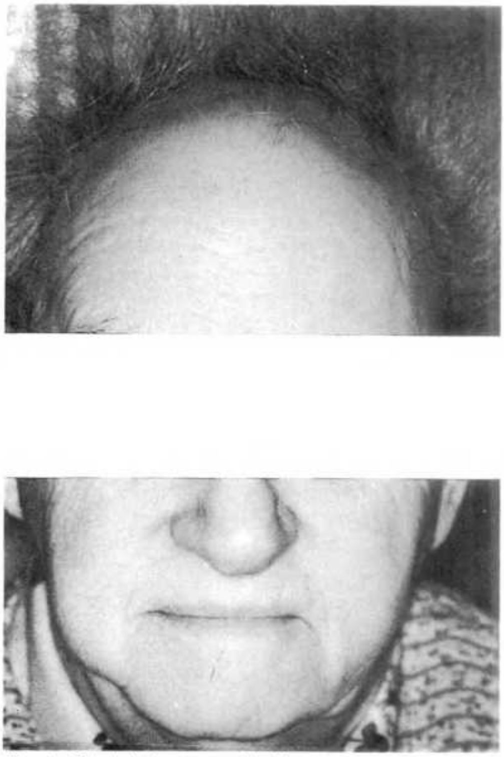

Fig. 1. Clinical features of baldness.

Table 1. Hormone levels before and after operation

	Pre-op	Post-op	Normal range
Free testosterone (pmol/l)	58·5 (52·0)*	6·9	1–12
Total testosterone (nmol/l)	11·7 (12·6)*	1·4	0–4
Luteinizing hormone (iu/l)	41	24	—
Follicle-stimulating hormone (iu/l)	95	89	—
Free thyroxine (pmol/l)	16·3	Not done	10–25
Free triiodothyronine (pmol/l)	7·2	Not done	3–9·5

*Repeat values in brackets.

with luteinized stromal cells. A close correlation between structure and function was apparent from the dramatic reduction in her high serum testosterone levels after surgery. Some authors have reported elevated levels of circulating oestrogen with virilizing tumours (Connor *et al.* 1968; Novak *et al.* 1970) and attributed this to extra-ovarian conversion of androstenedione in postmenopausal patients (MacDonald *et al.* 1976). However, most of these patients have a proliferative endometrium (Rome *et al.* 1981), unlike our patient. It might have been more informative to have compared steroid levels in the ovarian vein and in peripheral blood, as advocated by Bullon *et al.* (1981), but the data in Table 1 clearly implicate the ovary as the source of the excess testosterone.

The exact mechanism of hormone production by ovarian stromal cells is unclear. Virilizing tumours in pregnancy are readily attributed to high circulating human chorionic gonadotrophin (hCG) (Connor *et al.* 1968); in the non-pregnant state several theories have been advanced, each with its obvious limitations. The mechanical theory developed by Woodruff *et al.* (1963) suggests that pressure on adjacent stromal cells from an enlarging cyst induces luteinization in such cells. MacDonald *et al.* (1976) consider that the high luteinizing hormone levels in postmenopausal women induce functional activity in mitotic stromal cells encountered in ovarian carcinoma. High intracellular hCG concentrations in some tumours may explain their abnormal hormone production (Scully 1987).

Whatever the mechanism of abnormal hormone production, benign ovarian tumours with

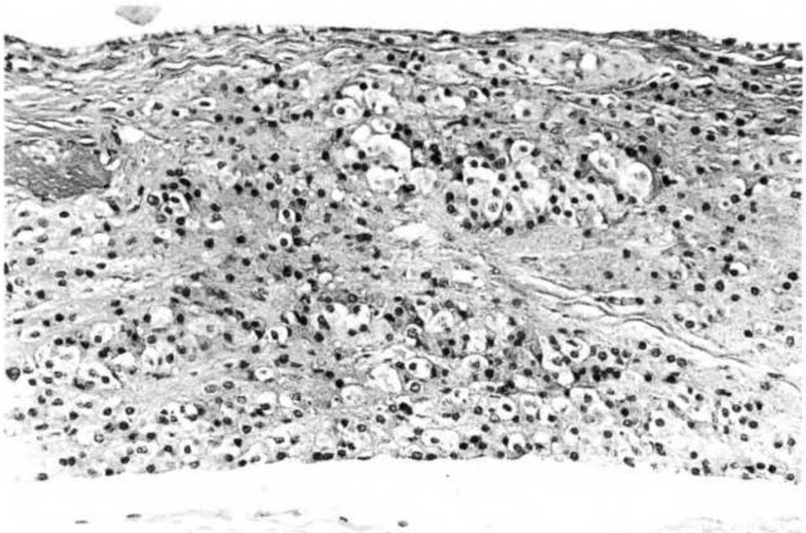

Fig. 2. The outer part of the ovarian cyst wall showing luteinization of stromal cells (haematoxylin and eosin).

a virilizing stroma are very rare, but the diagnosis should be considered in postmenopausal women with secondary alopecia.

Acknowledgment

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SHORT COMMUNICATIONS

The effect of smoking in pregnancy on maternal serum alpha-fetoprotein, unconjugated oestriol, human chorionic gonadotrophin, progesterone and dehydroepiandrosterone sulphate levels

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Bernstein *et al.* (1989) in a study of 147 women found that smoking in pregnancy was associated with reduced maternal serum human chorionic gonadotrophin (hCG) and oestradiol levels. Our own results on hCG and unconjugated oestriol (uE$_3$) are similar and we present them here, together with data on maternal serum alpha-fetoprotein (AFP), progesterone and dehydroepiandrosterone sulphate (DHEAS) which we also studied. All five are markers of fetal Down's syndrome and we examined levels in smokers and non-smokers to see whether, in antenatal screening, there was any advantage in taking account of maternal smoking.

Methods and results

Maternal serum samples at 13–27 weeks gestation from 77 Down's syndrome and 385 unaffected pregnancies had been measured for AFP, uE$_3$ and hCG (Cuckle *et al.* 1987; Wald *et al.* 1988*a*, 1988*b*), as well as for progesterone and DHEAS (yielding, respectively, median values for Down's syndrome of 1·20 and 0·88 multiples of the median (MoM) for unaffected pregnancies of the same gestational age ($P<0{\cdot}001$ for both progesterone and DHEAS)).

Details of the smoking habits of the 462 women in the study were not readily available in our records, so we measured the cotinine concentrations in spare maternal serum samples that had previously been diluted 48-fold for the hCG analysis, using a high sensitivity cotinine assay (Knight *et al.* 1989). Cotinine is a major metabolite of nicotine, and is widely used as an objective means of differentiating smokers from non-smokers. When diluted samples are assayed for

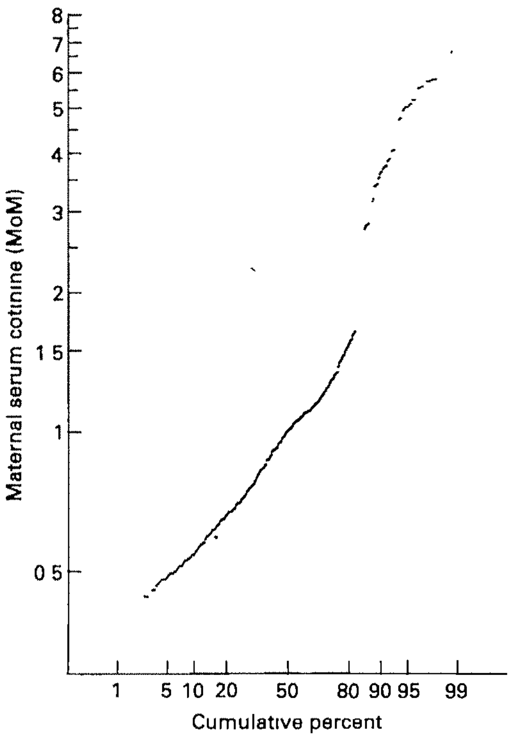

Fig. 1. Probability plot of centiles of maternal serum cotinine (log scale) in 462 pregnancies Maximum likelihood analysis was used to fit to the data the sum of Gaussian distributions from smokers and from non-smokers weighted according to the proportion of smokers (P) and non-smokers ($1-P$) in the population The probability density function $f(x)$ for a cotinine level, x, is given by:

$$f(x) = \frac{P}{\sqrt{2\pi}S_1}\exp\left(-\tfrac{1}{2}Z_1^2\right) + \frac{(1-P)}{\sqrt{2\pi}\,S_2}\exp\left(-\tfrac{1}{2}Z_2^2\right)$$

where· $Z_1 = (\log_e x - M_1)S_1$; $Z_2 = (\log_e x - M_2)/S_2$; M_1 and S_1 are the mean and standard deviation of $\log_e$ cotinine in smokers; and M_2 and S_2 the corresponding parameters for non-smokers. (MoM, Multiple of the median value for all samples combined)

Table 1. Maternal serum AFP, uE_3, hCG, progesterone and DHEAS level· 25th, 50th (median) and 75th centile (in MoMs) according to the cotinine smoking category* in unaffected and Down's syndrome pregnancies

		Unaffected pregnancies		Down's syndrome		Statistical significance
		Cotinine category		Cotinine category		
	Centile	Non-smoker ($n = 319$)	Smoker ($n = 66$)	Non-smoker ($n = 65$)	Smoker ($n = 12$)	Smokers *vs* non-smokers given type of pregnancy (P)
AFP	25	0·79	0·81	0·60	0·64	
	50	0·99	1·06	0·76	0·90	0·013
	75	1·21	1·36	0·91	1·33	
uE_3	25	0·83	0·77	0·59	0·56	
	50	1·00	0·95	0·73	0·71	0·20
	75	1·19	1·19	0·90	0·95	
hCG	25	0·75	0·67	1·52	0·94	
	50	1·02	0·91	2·06	1·51	0·034
	75	1·54	1·24	2·86	3·53	
Progesterone	25	0·86	0·77	0·93	0·88	
	50	1·00	0·94	1·20	1·04	0·028
	75	1·23	1·12	1·47	1·49	
DHEAS	25	0·71	0·86	0·56	0·71	
	50	1·01	1·15	0·86	1·11	0·046
	75	1·39	1·53	1·17	1·42	

* Women with serum cotinine levels ≥ 1·94 multiples of the median for all samples combined are categorized as smokers.

MoM, Multiple of the median value in unaffected pregnancies of the same gestation.

cotinine the value obtained includes both the cotinine level and a component attributable to the diluent and other non-specific factors. Consequently, cut-off levels normally used to separate smokers from non-smokers are not appropriate without first adjusting the cotinine values. Rather than subtracting an arbitrary amount to correct for the non-specific background, we used a maximum likelihood analysis to distinguish smokers from non-smokers (the precise method is described in the legend to Fig. 1), after expressing values as multiples of the median value for all samples combined. For this analysis results from affected and unaffected pregnancies were combined.

Figure 1, a probability plot of the distribution of log cotinine values, shows that a level of about 2 MoM readily separates the women into two cotinine populations—a large group of nearly all values under MoM and a small group with a distribution of much higher values. The precise cotinine level distinguishing putative smokers and non-smokers determined by the maximum likelihood analysis was 1·94 MoM. Cotinine levels ≥1·94 MoM included 98·8% of 'smokers' and only 1·4% of 'non-smokers'. The high degree of separation indicates that had the source of assay error due to the non-specific background not been present our results would not have been materially altered.

The results are shown in Table 1 The 25th centile, median and 75th centile values for AFP, uE_3, hCG, progesterone and DHEAS are given according to whether the cotinine level was ≥1·94 MoM or <1·94 MoM. The values are expressed in MoM units for unaffected pregnancies of the same gestational age. In pregnancies with and without Down's syndrome the 25th, median and 75th centiles of AFP and DHEAS were higher in the smokers than the non-smokers whereas those for uE_3, hCG and progesterone were lower. The differences in these levels between smokers and non-smokers were statistically significant for AFP, hCG, progesterone and DHEAS but not for uE_3.

Discussion

Our results on hCG confirm those reported by Bernstein *et al.* (1989) and, in addition, show differences in other fetal trophoblast metabolites that pass into the maternal serum.

When screening for Down's syndrome using maternal age, AFP, uE_3 and hCG as we have described (Wald *et al.* 1988*b*), allowance could be made for smoking by deriving separate medians for smokers and non-smokers to calculate MoM values. For example, if a 30-year-old smoker's

AFP, uE_3 and hCG levels were 0·70, 0·60 and 1·50 MoMs, respectively, the use of smoker-specific medians would change these values to 0·65, 0·67 and 1·68 MoMs, respectively. The estimated risk of having a Down's syndrome term pregnancy would increase from one in 250 to one in 200 assuming that the age-specific risk of Down's syndrome were the same in smokers and non-smokers, an issue that is still unresolved (Hook & Cross 1988), and that for each marker the magnitude of the smoking effect in affected pregnancies were the same as in unaffected pregnancies. While allowance for smoking could have a material effect on the risk estimates among individual smokers, it would only have a negligible effect on the overall detection and false-positive rates of the screening programme. Although the variance of each marker would be reduced by removing one source of extraneous variation, the reduction would be very small (a maximum of 0·2%). The effect on average screening performance would not *itself* justify introducing the complexity, but because of the effect on the risk estimate for some individuals, some centres in which information on smoking is readily available may wish to use separate medians for smokers and non-smokers.

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Infection with the Puumala virus in pregnancy. Case report

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Case report

A previously healthy 29-year-old woman was admitted in her second pregnancy at 17 weeks gestation because of an acute, high fever up to 39·5°C, headache, abdominal pain and myalgia. She had been ill for 5 days. These clinical features led first to an exploratory laparotomy and the removal of a healthy appendix. After the operation, proteinuria up to 3·2 g/day for 4 days and transitory azotaemia with a serum creatinine up to 433 μmol/l were observed. There was also a thrombocytopenia of $47 \times 10^9/\ell$ and polyuria up to 4400 ml/day. The clinical diagnosis of typical, moderate nephropathia epidemica was made. The diagnosis was confirmed by seroconversion to the Puumala virus (IFAT) (Lähdevirta *et al.* 1984). The woman recovered within 4 weeks. During the illness a living normal fetus was seen by ultrasound. The pregnancy continued uneventfully and ended in vaginal delivery at 39 weeks gestation. A healthy boy, 3500 g in weight and 49 cm in height, was born. The Puumala virus antibody titres in the baby were 1:80 in umbilical vein blood, 1:40 at 2 months, and 1:20 at 5 months. These were considered to be passive antibodies from the mother, because the total IgM level in cord blood was <0·3 g/l and simultaneous maternal titres were 1:80 at delivery, 1:160 at 2 months, and 1:80 at 5 months after delivery. At the age of 5 months the child was well and normal on clinical examination.

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Discussion

Nephropathia epidemica belongs to the group of diseases called haemorrhagic fever with renal syndrome (HFRS). They are caused by Hantaviruses which have different rodents as reservoirs. Clinically and aetiologically there are three different diseases which are widely spread in Asia and Europe (Johnson 1989). The most severe form of them, Korean haemorrhagic fever (KHF) is caused by Hantaan virus and occurs mainly in Korea, China and Eastern Siberia. A less severe form is caused by Seoul virus and occurs additionally in Japan. The mildest form is caused by Puumala virus and occurs in Scandinavia, in European part of the USSR and in Central Europe. The clinical features of nephropathia epidemica were described by Lähdevirta (1971). The main differences between nephropathia epidemica and Korean haemorrhagia fever are the lower mortality (<0·5% compared with 5–10%) and the less pronounced haemorrhagic manifestations in the former. The main natural reservoir of Puumala virus is bank vole (*Clethrionomys glareolus*). The transmission to humans probably happens by inhalation of dust contaminated with urine and faeces of the vole. Human-to-human transmission is not known to occur.

There are only two reports available about the effects on pregnancy of Korean haemorrhagic fever and none about those of nephropathia epidemica. In the first report Korean haemorrhagic fever caused a miscarriage at 7 months and the fetal organs showed histological changes similar to those seen in adults, indicating transplacental infection (Kim *et al.* 1978). The second report described a successful pregnancy with a healthy baby (Chae *et al.* 1989).

Our case report shows that, in areas where it occurs, haemorrhagic fever with renal syndrome should be considered in the differential diagnosis of acute febrile illnesses during pregnancy. The diagnosis is based on the clinical findings and can be confirmed serologically. Even if the woman recovers fully, there is uncertainty as to whether the infection is harmful to the fetus. In Korean haemorrhagic fever transplacental infection occurs and risk of miscarriage is high. Although nephropathia epidemica is less severe than Korean haemorrhagic fever, it is not possible, on the basis of our patient, to assess the risk to the fetus.

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Malignant fibrous histiocytoma of the fallopian tube

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Case report

A 54-year-old postmenopausal, married, nulliparous woman presented with a sudden onset of right iliac fossa pain. She also complained of a vaginal discharge, dyspareunia and an episode of postcoital bleeding. She was apyrexial and her general condition was satisfactory. Tenderness was noted over the lower abdomen. A cystic mass was palpable in the right iliac fossa. Apart from a raised ESR of 86, all results of haematological

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and biochemical investigations were normal. Laparoscopy revealed a right-sided pyosalpinx with pus at the fimbrial end. The left tube and both ovaries were normal. A diagnosis of acute pyosalpinx was made and the patient was given ampicillin and metronidazole. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were arranged for 6 weeks later.

Four weeks after discharge the patient was readmitted complaining of severe back pain and night sweats. There had been a weight loss of 10 kg. Her ESR had risen to 137. On examination the patient appeared unwell and a tender suprapubic mass was noted. At subsequent laparotomy a large right-sided mass was found measuring 15 × 17 × 12 cm which appeared to originate in the right fallopian tube. It was not totally encapsulated and was adherent in some areas to omentum and small bowel. The uterus was enlarged with several intramural fibroids. The liver and pouch of Douglas appeared normal. The mass on the right side was freed and a total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. As the mass appeared malignant, an omentectomy was also performed. Internal and external iliac, deep and superficial inguinal lymph nodes were sampled for staging purposes; macroscopically none was involved. A malignant fibrous histiocytoma of the right fallopian tube was diagnosed at histopathology. Chest X-ray and liver function tests showed no evidence of metastasis.

The patient was reviewed by the oncologist 5 weeks after operation with a view to adjunctive chemotherapy. On examination the patient was found to have a recurrence of the mass in the abdomen. She was given a regimen of ifosfamide, 5 g/m^2, with Mesna rescue and epirubicin, 75 mg/m^2. An abdominal ultrasound revealed a large soft tissue tumour extending from the pelvis to 3 cm above the umbilicus. It was multiloculated and mainly solid. No hydronephrosis was noted and the liver was normal. As there was a poor response to chemotherapy the patient was referred for radiotherapy. A total dose of 4000 cGy given over 20 treatments was administered. After radiotherapy, an abdominal ultrasound showed a right-sided mass (15 × 12 × 7·5 cm), enlarged para-aortic nodes and a large mass anterior to the left kidney. Chest X-ray showed a left pleural effusion. A liver/spleen scan revealed diffuse filling defects. Disseminated disease was confirmed. The patient died 21 weeks after her initial presentation.

Discussion

On review of the literature there are no reports of a malignant fibrous histiocytoma originating in the fallopian tube (Kearny *et al.* 1980; Weiss & Ensinger 1978). This sarcoma was probably misdiagnosed as a pyosalpinx at laparoscopy. Given its subsequent behaviour, it is probable that earlier debulking would not have altered the prognosis. The malignant fibrous histiocytoma is the most common soft tissue sarcoma of late adult life (Fletcher 1987) and occurs between the ages of 50 and 70. This tumour was of the giant cell subtype—a variety with an incidence of between 5 and 15% (Lawson 1987). There are few data on the aetiological factors in this disease. It is a matter of controversy whether adjunctive chemotherapy is beneficial in soft tissue sarcomas, and neither chemotherapy nor radiotherapy made any impact on the course of this condition. Despite total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, negative sampled lymph nodes, chemotherapy and radiotherapy this patient died from disseminated disease 21 weeks after her initial presentation.

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CORRESPONDENCE

Uterine activity during spontaneous labour after previous lower-segment caesarean section

Dear Sir,

Arulkumaran *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 933–938] describe quantification of intrauterine pressure by integration of its recording, which I and others did in the early 1970s. While this calculation of uterine activity was able to separate the various pathological labour groups, in my experience it was of no more clinical use than uterine palpation in the individual patient.

I doubt the authors' claim that 'The use of an intrauterine catheter provides accurate information and enables the uterine activity to be computed' for a simple reason. Once the membranes are ruptured, the intra-amniotic cavity is no longer a closed system and Pascal's law does not apply. With leakage of fluid, there can be isolated pockets of different intrauterine pressures during contractions.

For as stated by Csapo (1970), 'When an open catheter is placed intra-amniotically from below, through a micropuncture of the amniotic membrane, the intrauterine pressure is accurately recorded for a short period until the leakage of amniotic fluid seriously distorts it'. Neuman *et al.* (1972) monitored 12 parturients with two transcervical catheters and one intrauterine pressure transducer simultaneously. These investigators found a coefficient of variation >23% in intrauterine pressure recordings, and concluded that 'no single uterine pressure observation is an accurate reflection of uterine pressure during labor'.

Using either multiple open intrauterine catheters or solid transducer-tipped catheters, I have found 15–28% variations in pressure readings between two recorders in the same uterine contraction. Given the interest in the use of uterine-work calculation technique in Europe, I believe that these investigators should confirm their assumptions of the precision of intrauterine pressure recordings after membrane rupture before proceeding with future studies.

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Authors' reply

Dear Sir,

We thank Dr Goodlin for his comments. In the absence of a reference we have been unable to trace his work to which he alludes.

His quotation from the paper by Csapo (1970) is incomplete; in the same paragraph Csapo states 'The changes observed in intrauterine pressure are determined by the extent of rupture, the position of the mother and the leakage control of the fetal head. Only when the descending head completely prevents the leakage of amniotic fluid is the loss of pressure corrected'. Neuman *et al.* (1972) compared pressures derived from fluid-filled catheters with those from an intrauterine sensor. They showed only slight differences between these methods which are understandable given the inherent inaccuracy of fluid-filled devices.

The intrauterine catheter provides information about the pressure within the pocket in which the transducer tip is lying. This pressure may not be representative of the entire intrauterine cavity if there are different pockets of amniotic fluid. However, if the transducer tips lie in different pockets, the fact that these catheters passed transcervically reached these spaces suggests that there is some communication at least by a film of fluid and the pressure should be equal according to Pascal's law. Steer *et al.* (1978) compared the simultaneous pressure readings from a Gaeltec catheter and fluid-filled catheter in four women and found a coefficient of variation similar to that reported by Neuman *et al.* (1972). In our institution we have compared the Gaeltec catheter with the fibre-optic catheter in ten women. The tracings were identical in most cases and the coefficient of variation was <10%.

Differences between our findings and others might be due in part to the fact that the fluid-filled catheter produced suboptimal readings due to the possibility of blockage or compression. Certainly this fact needs further study. Dr Goodlin's comment that 'it is of no more clinical use than uterine palpation' or even external tocography has to be verified by randomized clinical studies and such a study is nearing completion in our institution. It is our opinion that it is useful when external tocography is not satisfactory. The importance of recording uterine contractions, especially with the use of oxytocic drugs in a woman with a scarred uterus is obvious, especially in the litigious climate of obstetrics today.

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Nausea and vomiting of early pregnancy and pregnancy outcome. An epidemiological study

Dear Sir,

I read with interest the article by Weigel & Weigel [*Br J Obstet Gynecol* (1989) **96**, 1304–1311] about nausea and vomiting of early pregnancy. I agree with the authors that nausea and vomiting should be treated separately. Nausea is a subjective symptom whereas vomiting is objective and, as the authors have shown, they carry different clinical significance. However, the vomiting patients should be subdivided into emetic and hyperemetic groups. For those patients whose vomiting leads to severe weight loss, dehydration and electrolyte disturbance (the hyperemetic group), there is a higher chance of fetal growth retardation (Chin & Lao 1988; Gross *et al.* 1989). Thus although the number of hyperemetic patients in the present series may be small, they should still be separated from the group with lesser degree of vomiting because the conclusion that vomiting patients are at no higher risk for producing small-for-dates babies may not apply to the hyperemetic patients.

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Pregnancy screening by Doppler uteroplacental and umbilical artery waveforms

Dear Sir,

I read the article by Hanretty *et al.* [*Br J Obstet*

Gynaecol (1989) **96**, 1163–1167] with interest, but I was disappointed by the summary of their findings. An obstetric population was screened (543 patients) with no attempt to select on the basis of risk factors. The incidence of subsequent fetal/neonatal morbidity was, not surprisingly, low. The statistical power of such a small series is low and the authors acknowledge this point. Yet they are prepared to conclude that their results do not support the use of Doppler in clinical practice. The authors are not justified in making this conclusion. They have demonstrated only that in a small unselected obstetric population an abnormal umbilical Doppler study was associated with lower birthweight. The use of Doppler as a screening test in such a low-risk population is quite a different issue to the use of Doppler in the management of high-risk pregnancy. In the latter situation the presence of risk factors, the recognition of complications which might threaten fetal welfare, or the clinical suggestion of small fetal size indicate a much higher risk of fetal compromise. They are associated with quite a different incidence of adverse fetal outcome.

There are many reports of the use of Doppler in high-risk pregnancies which demonstrate strong statistical associations between an abnormal result and abnormal outcome. The authors reference some of these studies and suggest their findings should be compared with these. Such studies are in fact quite different in design. It is proper for the authors to suggest the need for randomized trials over and above the one that has already been reported. It is not proper for the authors to reject the use of Doppler in clinical practice.

I also have a methodological concern with this paper. The authors made no use of real-time ultrasound to aid Doppler screening. There are patients in whom the umbilical signal is difficult to detect, and the ability to see a loop of cord for determining the line of insonation and optimizing the signal is necessary. Without this facility a low amplitude signal may be obtained in which diastolic velocities are removed by thump filtering. I am very surprised that the authors identified six patients with absent end diastolic flow velocities at 34–36 weeks and subsequent normal outcome. This is quite different to our experience (unreported) screening 500 normal pregnancies (no such cases).

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Authors' reply

Dear Sir,
The study which we performed was intended to address the issue of screening an unselected population. Techniques introduced into obstetrics as being of value in high-risk pregnancy are inevitably extended to unselected populations. This was the case with electronic fetal monitoring and seems likely to happen with Doppler.

Furthermore, the vascular pathologies underlying abnormal waveforms might theoretically be detectable before patients are identified clinically as being high risk. Thus there appeared to be potential for the use of Doppler as a screening technique. This was the justification for our study.

We do, however, agree with much of what Dr Trudinger says, except that we did not conclude that Doppler is not potentially valuable in clinical practice: merely that its role is not yet clear nor its value proven.

The finding of absent end diastolic flow in association with a normal outcome was surprising for us also and in contrast with our observations in high-risk pregnancy. The thump filter on the machine used was relatively high (300 HPVz), but when repeated using a filter of 150 the finding of absent end diastolic velocity was again confirmed. This finding requires further investigation.

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BOOK REVIEWS

Statistics with Confidence. Confidence Intervals and Statistical Guidelines by Martin J. Gardner & Douglas G. Altman. British Medical Journal, London, 1989, 140 pages, UK £7.95, overseas £9.50, USA $19.00 including postage by air. Can be ordered from the British Medical Journal, PO Box 295, London WC1H 9TE

As a reviewer of papers submitted for publication in a variety of journals, I am often in the position of requesting authors to improve their work by giving an indication of the precision of their sample estimates. However, until the publication of this book by Martin Gardner and Douglas Altman, I could not point such authors to an easily understandable book which would not only show them how to calculate confidence intervals, but would also explain the rationale behind them, and their appropriateness for particular circumstances. Now this gap in the market has been admirably filled. Many of the chapters are based on published articles, but these were previously scattered over a number of different journals. Here they have been revised and collected together with some additional chapters especially written for the book.

A further bonus is the availability of a computer program on floppy disk, with an accompanying manual, which can be used to perform the calculations with relative ease (*Confidence Interval Analysis:* £65.00 (£45.00 for educational establishments, research institutes and the National Health Service) including VAT and post and packaging).

The book alone will surely become a standard reference in this field, and, with the computer program as an optional bonus, it is a package that few readers of or writers for journals could afford to be without.

Diana Elbourne

Dictionary of Abbreviations in Medical Science by Rolf Heister. Springer-Verlag, Berlin, Heidelberg, London, 1989, 287 pages, DM 58.00

Editors have a dislike for abbreviations in papers, not just because they are the ultimate form of jargon but because they may so often confuse and mislead.

If anybody is in any doubt about the confusion they can cause let them consult this *Dictionary of Abbreviations*. It begins with 18 entries for A (absorbance to axis) but the record seems to be held by PA with 29 possible meanings from atrial pressure to pulmonary artery. Even the widely used abbreviation AVP which we have published in this journal for arginine-vasopressin, can also mean antiviral protein, aortic vale prolapse, aortoventriculoplasty and arterial volume pulse. And politicans should note that EEC not only stands for European Economic Community, but European Endometriosis Classification. This book may occasionally be useful to somebody trying to understand an abbreviation-ridden paper, but its main value is as an AW (awful warning) never to use abbreviations.

F. E. Hytten

The Baby Under 1000 g edited by David Harvey, Richard W. I. Cooke & Gillian A. Levitt. Wright, London, 1989, 353 pages with figures and tables, £65.00

Babies under 1000 g are surviving in increasing numbers, usually at great cost both emotionally and financially to their families and carers. The subject of the symposium which preceded this publication is therefore an important one which will be of interest to all disciplines involved in the hospital care of mothers and babies. In the past few years there has been an avalanche of books on neonatal intensive care and various specific aspects of neonatal medicine. British authors and editors have now contributed a number of long-awaited, excellent comprehensive volumes covering the physiological/anatomical basis of perinatology and practical neonatal intensive care as practised on this side of the Atlantic.

It seems a pity therefore that, with such a title, the chapters of this multi-authored book vary considerably in the extent to which the author has confined himself to aspects of neonatalogy particularly relevant to the extremely low birthweight infant below 1000 g. Much of the information, albeit presented in a very readable form, is already available in other recent general textbooks of neonatology which would be easily accessible to readers of a book of this nature. Some of the shorter chapters, such as those addressing the hazards of the immature skin, metabolic problems, renal function and long-term outcome therefore stand out as being particularly pertinent and erudite in reviewing the currently available research data or state-of-the-art practical management of this extremely difficult group of babies. Chapters 2 and 3, dealing with obstetric management and mode of delivery, are excellent and should be obligatory reading for any obstetrician or midwife contemplating delivery or transfer of the very immature fetus.

Sadly this book, which contains much useful information for obstetricians and paediatricians, is rather overpriced compared to other more comprehensive textbooks of neonatology.

R. M. Thomas

Diagnosis and Therapy of Fetal Anomalies (Clinics in Diagnostic Ultrasound 25) edited by John C. Hobbins & Beryl R. Benacerraf, Churchill Livingstone, New York, Edinburgh, 1989, 324 pages with figures and tables, £35.00

Non-subscribers to any of the *'Clinics in . . .'* series are at times attracted to a single issue for an authoritative review. In this regard, Volume 25 of this series, catering for radiologists, may be of interest to obstetricians.

Birnholz's chapter on fetal syndromes bears witness to his skills in fetal portraiture. Benacerraf's effort on the sonographic signs of aneuploidy is authoritative if a little one-sided on femur length and nuchal thickness in screening for Down's syndrome. The chapter on anatomy is not for L drivers, demonstrating beautiful views of coronary arteries, fingernails, and palm creases, which the author states, in a broadside at the marketing of 'computed sonography' machines, can be obtained with everyday equipment. The usual division of chapters by organ systems prevails, although their order seems illogical, with anatomy left till Chapter 5, neural tube and CNS abnormalities sited seven chapters apart, and the sonography of aneuploidy being discussed before the relevant structural anomalies. The relevance to fetal anomalies of a chapter on the placenta is questionable, especially as it concentrates on grading. Only one of the 12 chapters deals with therapy, a sad reminder that our therapeutic skills lag well behind those in diagnosis. This examines only three conditions: red cell alloimmunization, obstructive uropathy, and hydrocephalus, making no mention of pleural fluid drainage. The therapy of fetal tachyarrythmias is alluded to in another chapter, in which it is afforded scant attention, mentioning the drugs used in four sentences, but not mentioning whether administered to the mother or the fetus.

The degree of detail varies between chapters: the excellent contribution on skeletal anomalies exhaustively tabulates the features of obscure dysplasias such as the Nievergelt type of mesomelic dwarfism, whereas the cardiac chapter is more generic, scarcely mentioning half a dozen examples of structural heart disease. The editing is also variable. We are told there are no established measurements for the thorax, yet in another chapter detailed referenced charts are given for thoracic length and circumference. The nine pages in the uropathy chapter dealing with lower urinary tract obstruction are largely repeated in the chapter on invasive therapy. Ultrasound-guided fetal blood sampling is illustrated separately in three chapters. The 100% false-positive rate for the lemon sign in open spina bifida is presumably a proofing error, while the 5% fetal loss rate quoted for needling the fetal peritoneal cavity or bladder seems extraordinary. Neologisms such as *placentocentesis* for chorion biopsy (c.f. *placentesis* used for obtaining blood from chorionic plate vessels), renocentesis, vesicocentesis and perinate reflect the predominantly transatlantic authorship.

This book should be excellent, given the eminence of the 23 contributors, but is let down by weak editing. Many of the pictures will be familiar to those conversant with the ultrasound literature. Indeed three of the contributors and one of the editors of this tome are co-editors of the current bible in the field. Although this may prove a handy review for some, it is not pitched at the beginner, and experienced practitioners will have already purchased more definitive texts.

Nicholas M. Fisk

Government Policy and Women's Health Care: The Swedish Alternative edited by Gunnela Westlander & Jeanne Mager Stellman. Haworth

Press, New York, London, 1988, 180 pages, $34.95

This is an interesting collection of papers about Swedish women edited by two female professors. Gunner Westlander also heads the Division of Social Psychology at the National Institute of Occupational Health in Stockholm, and Jeanne Stellman, an American, founded and directs a Woman's Occupational Health Resource Unit at Columbia University.

The chapters relating to repetitive strain injury, computers and the place of women in trade unions are of less relevance to gynaecologists than those relating to the arrangements for maternity care and Anita Hagstad's survey of gynaecological problems and sexuality in middle-aged women. Maternity benefits and parental leave, like employment and abortion law, are far in advance of our own provison and legislation. The factual and imaginative accounts of the changes in attitude towards sex education, contraception and abortion make fascinating reading and would be a good introduction to the emotive topic of fertility control for medical and nursing students and pupil midwives.

The impressive way in which the collection of government statistics has been changed to illuminate the problems of women, and the process of tackling health and employment problems by democratic discussion followed by appropriate legislation, would make this book a worthwhile addition to medical school and university libraries.

Wendy Savage

Books received some of which may be reviewed at a later date

Recent Advances in Obstetrics and Gynaecology. Number 16 edited by John Bonnar. Churchill Livingstone, Edinburgh, 1990, 296 pages fully illustrated, £19.95.

Reconstructing Babylon: Essays on Women and Technology edited by H. Patricia Hynes. Earthscan Publications Ltd, London, 1990, 239 pages, £8.95.

Biopsy Pathology of the Endometrium by C. H. Buckley & H. Fox. Chapman & Hall Medical, London, 1989, 289 pages fully illustrated, £55.00.

Clinical Cytotechnology by D. V. Coleman & P. A. Chapman. Butterworths, London, 1989, 484 pages fully illustrated, £65.00.

Fetal and Neonatal Body Fluids: The Scientific Basis for Clinical Practice (Reproductive and Perinatal Medicine X1) edited by Robert A. Brace, Michael G. Ross & Jean E. Robillard. Perinatology Press, Ithaca, New York, 1989, 372 pages with figures and tables, $105.00.

Urinary Tract Infection and Inflammation by Jackson E. Fowler Jr. Year Book Medical Publishers, Inc., Chicago, London, Boca Raton, 1990, 339 pages with figures and tables, £55.50.

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Antenatal Teaching. A Guide to Theory and Practice by Patricia Wilson. Faber & Faber, London, Boston, 1990, 205 pages illustrated, £4.99

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COMMENTARY

Perinatal audit: does confidential enquiry have a place?

Medical audit is of growing importance. After a period of increasing interest in the profession in developing more systematic audit of clinical practice the subject has been highlighted as one of the central proposals in the Government's white paper 'Working for Patients' (DH 1989); this proposal is one of few in the white paper to meet with immediate and full acceptance by the medical professional bodies. Confidential enquiry into deaths has figured more or less prominently in the better-known examples of medical audit to date, with particular emphasis on the scrutinizing of cases for instances in which clinical care might fall short of accepted standards. This approach was pioneered by the Confidential Enquiries into Maternal Mortality (DH 1989) which termed a 'departure from the accepted standards . . . which may have played a part in the ensuing death' an avoidable factor. Notably, this general method was also followed by the largest systematic review of deaths in this country, the Confidential Enquiry into Perioperative Deaths (Buck *et al.* 1988). Systematic regional perinatal mortality surveys are to be instituted by 1991, and the place of confidential enquiry into some categories of perinatal death is to be considered (Chalmers 1989).

According to one's point of view, it is either ironic or inevitable that the speciality which was first to introduce the notion of the avoidable factor in the audit of deaths should be the first to question seriously its basis, as applied to perinatal mortality. There seem to be three main interrelated objections concerning, respectively, the specification of accepted standards, the establishment of a causal link between an avoidable factor and the subsequent outcome, and the relative importance of a particular factor in the perhaps complex web of events preceding death.

Firstly, the notion of accepted standards is undeniably rather loose: one person's accepted standards may be no more than outdated ritual to another. It would be unrealistic to attempt to predefine a comprehensive set of responses appropriate to every circumstance which may arise in obstetric practice. Given that the accepted standards cannot be exhaustively itemized before the event, the objection then depends crucially on whether or not assessors can meaningfully determine departures from accepted standards after the event. Evidently those who conduct, participate in, and publish the various confidential enquiries believe that they can; this must include the great majority of obstetricians and gynaecologists who participate in enquiries into maternal mortality and perioperative deaths, and generally meet with approval rather than criticism for so doing (Black & McKee 1988). There seems no immediately apparent reason why obstetric practice in relation to perinatal mortality should constitute an exception.

The second objection to the concept of the avoidable factor is that the existence of a direct causal link between a particular course of action and a subsequent death may not be sufficiently established to be convincing. When considering causation epidemiologically, a spectrum of strength of evidence may be recognized, ranging from the weak suggestion arising from association alone, through various degrees of inferential evidence, to the strong demonstration afforded by blind controlled intervention studies. One approach might be to accept a particular act of commission or omission as an avoidable factor only if suitably conducted double-blind randomized trials have shown it to result in a significantly higher probability of perinatal death. Whilst undoubtedly rational, this approach would suffer from some practical drawbacks. A large number of interventions have not yet been assessed in this way and, whilst the drive to continue to reduce their numbers should be supported strongly, it would be an abdication of responsibility simply to refuse to form judgements based on currently available evidence in all such cases. Furthermore, it may never be practically possible to assess some established interventions to this standard, because of ethical objections where strong circumstantial evidence of high effectiveness exists. In the audit of maternal mortality, there could be few who would not agree that failure to give antibiotics to a patient with confirmed septicaemia would constitute an avoidable factor, and yet this intervention has never been subjected to a controlled trial against placebo. In perinatal mortality, as in other fields, there is individual disagreement about exactly where the line between acceptable and unacceptable practice should be drawn. Assessors must take account of this when determining departures from accepted standards. In other words, if the level of evidence surrounding an intervention is such that its use may reasonably be regarded as optional, failure to use it must not be assessed as an avoidable factor. That assessors can make the distinction has been confirmed by a blind case-control study (Niswander *et al.* 1984) which showed significant associations between some categories of care assessed as suboptimal and adverse outcomes; although suboptimal care was associated with proportionately few instances of adverse outcome, adverse outcome was three to four times as likely in the presence of suboptimal care.

The third objection depends on the observation that an identified factor is not uncommonly only one of a number of physiological insults preceding a death; this may be more common in the case of perinatal death, particularly where the baby is very small, but is certainly not unique to it. The subsequent death may then be more related to other events; it may have occurred regardless of the avoidable factor, or the avoidable factor may only have led to death because of the occurrence of other events. A 'departure from accepted standards . . . which may have played a part in the ensuing death' is clearly a long way from the idea of a necessary and sufficient cause; it would therefore be illogical to discard the concept because an individual factor may have been neither necessary nor sufficient for the ensuing death. This objection has been stated in various forms: 'Who can tell whether a perinatal death could have been avoided?' (Baird 1980); ' . . . no one can know whether the absence of the "avoidable" factor would have prevented the death . . . ' (Macfarlane 1984). The quotation marks surrounding 'avoidable' in the second example highlight a common misconception: it is the factor which is described as avoidable, and not the ensuing death.

It seems then that the concept of the avoidable factor is no more and no less applicable to perinatal mortality than to other forms of mortality audit. The limitations must be clearly recognized, and the definition promulgated by the Confidential Enquiry into Maternal Mortality is admirable in drawing attention to these. Within this definition, there is a framework to review examples of adverse outcomes in retrospect, not to attribute causation but to audit the clinical practice. The fruitfulness of such an approach, of course, still depends on the potential of clinical practice to modify the probability of the adverse outcome monitored; there would be little relevance in auditing clinical care against standards related to avoidance of mortality in an area where death will occur regardless of medical intervention, since the objectives of the care would be different in these circumstances. In the case of perinatal mortality, this could apply to the management of lethal congenital malformation or extreme immaturity, and such instances may be better excluded from a confidential enquiry.

Theoretical objection to the approach is clearly not the only cause of the local opposition not uncommonly evinced to the suggested inclusion of avoidable factor assessment in perinatal mortality surveys. There are other understandable reasons. The exposure of personal performance to scrutiny by others is never comfortable, and the approach may be perceived as critical in its comparison with standards. The feeling of discomfort is exacerbated by the fact that the original decisions probably had to be taken rapidly in difficult circumstances and with incomplete information; in contrast the review was made at leisure with the benefit of hindsight. The flame of incipient resentment is doubtless fanned by the bias inherent in the sample of practice reviewed, which by its nature will over-represent problems of clinical management and under-represent successes. Individual clinicians may feel that external review is unnecessary because any lessons to be learned have already been appreciated without any outside assistance. Fears of litigation may be raised, and survey organizers may be concerned about decreased notification of cases.

Faced with these responses, it would not be surprising if many would-be investigators simply abandoned the idea of including an avoidable factor assessment when planning studies. Even when such an assessment has been carried out, further difficulties may arise in gaining consent to publish the summary findings, and permission may be subject to strict provisos concerning description of the factors and events. Consequently the writers tend to dilute their descriptions of the case so that readers may question the relevance of the factors so insubstantially described (and as a result perhaps reawakening doubts about the underlying concept, and restarting the cycle). This dilemma is particularly poignant for the investigators who were acutely aware of the defects in the management of the cases before the distancing process removed the details. It is difficult to sustain theoretical doubts over clinical relevance on recalling that the case sheet showed, but has not been quoted as showing, that the fetal heart rate pattern was very abnormal (to auscultation as well as on trace) for over 6 h during which repeated calls to obstetric staff met with no response; or on recalling that the records described the doctor as repeatedly attempting to carry out a forceps delivery over a 3 h period before summoning further help.

It seems that the audit of clinical practice by confidential enquiry may be as valid in the field of perinatal mortality as elsewhere, no more and no less. Such confidential enquiries would be most fruitful if applied to groups of perinatal deaths most likely to show scope for prevention through clinical practice, and the approach can then make a valuable contribution to perinatal audit. Although an understanding is required of the implications and limitations of the approach, and in particular that the management and not the outcome is being audited, rejection of the concept is unwarranted. To do so at this time of heightened awareness of the needs for medical audit would be to lose a major opportunity in a field where obstetricians have led the way.

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The obstetric forceps—are we using the appropriate tools?

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Summary. A total of 166 pairs of obstetric forceps of three different types in regular use in two major obstetric units was measured and compared with manufacturers' master instruments and drawings. As well as linear measurements of blade, shank and handle the distances between the tips and maximum distance between the blades, and the mean radius of the cephalic curve were determined. The purpose of the study was to assess the suitability of instruments in common use for present day practice. It was found that the measurements differed significantly from the original descriptions and there were wide variations between instruments of the same type, even when supplied by the same manufacturer. In some cases the blades had not been packed in matching pairs in the Central Sterile Supplies Department. It is suggested that critical reappraisal of the forceps in current use in many obstetric units is overdue. As well as a need for reconsidering the type of forceps used the dimensions of individual pairs should be checked.

It is over 250 years since the obstetric forceps came to be a standard part of the obstetrician's armamentarium and the mechanical principles have stood the test of time, although the manner and purposes of use have changed.

Initially forceps were made to individual physician's requirements by the village blacksmith or by master cutlers. Later, specialist surgical instrument makers evolved, usually based close to, and relating with, major teaching hospitals.

Traditional methods of manufacture by hand forging have generally continued, in most cases using master patterns and rarely working to mechanical drawings. In consequence various modifications have crept in, almost unnoticed, and generally have been uncritically accepted by obstetricians.

Obstetric units in the United Kingdom are commonly equipped with three types of forceps.

1. Short forceps of the Wrigley type. Wrigley (1935) described his 'short light forceps for delivery of the low foetal head'. He was concerned with the high rate of forceps delivery and the inappropriate design of the instruments used. His forceps have short handles and shank so that it is impossible to apply them to a fetal head that is not well down in the pelvic cavity, nor is it possible to exert undue compression or traction forces.

2. Kielland. Kielland (1915) first described his forceps with very precise measurements laid down. Genuine instruments to his specification bear the stamp 'Original Kielland' but copies from other manufacturers are more commonly used.

3. A long forceps based on designs often originating over a century ago, such as Simpson in 1848, Barnes in 1864 or Anderson circa 1878, and in Scotland, Haig Ferguson in 1911 or

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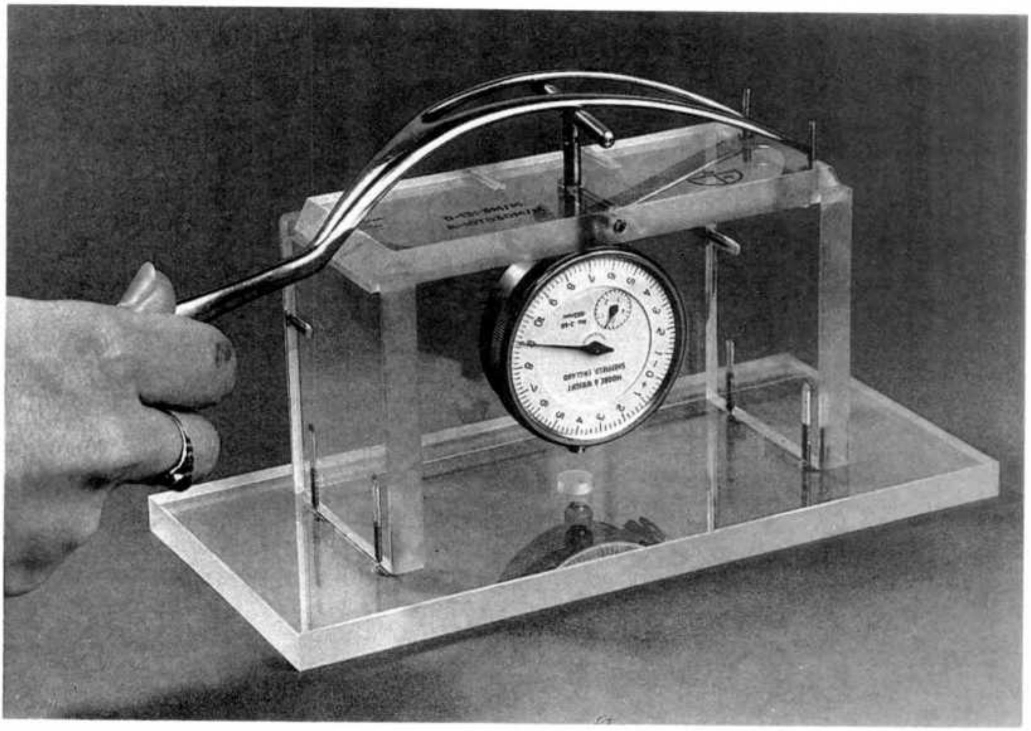

Fig. 1. The device for measuring the radius of curvature of forceps.

Milne-Murray in 1891 (see Hibbard 1988). Commonly the Barnes and Anderson forceps were originally fitted with a Neville axis traction rod but in most cases the rod has been discarded subsequently. The long forceps in use often referred to as Barnes forceps in fact owe more in design and measurement to Anderson. At least one instrument supplier currently markets an Anderson type of forceps under the name of Barnes.

Materials and methods

Overall 166 pairs of forceps were captured from circulation in the delivery units of the hospitals in South Glamorgan before being returned to

Table 1. Measurements of forceps in use in Cardiff*

	Wrigley (57 pairs)			Kielland (52 pairs)			Anderson (57 pairs)		
	Mean	(SD)	Range	Mean	(SD)	Range	Mean	(SD)	Range
Overall length	271	(5·11)	260–285	397	(8·70)	370–414	371	(2·71)	368–382
Handle length	72	(2·34)	67–75	105	(8·22)	98–138	138	(1·21)	135–140
Shank length	55	(4·05)	46–62	116	(10·59)	110–128	79	(4·04)	70–86
Blade length	144	(3·92)	137–157	176	(8·23)	146–192	154	(4·31)	148–164
Between tips	24	(2·14)	16–28	24	(4·43)	15–37	27	(3·75)	22–47
Maximum between blades	79	(2·16)	76–83	85	(3·40)	77–92	82	(6·83)	76–96
Cephalic curve—mean radius	113	(6·56)	101–132	125	(8·70)	111–148	124	(8·66)	113–145

*All measurements are to the nearest mm.

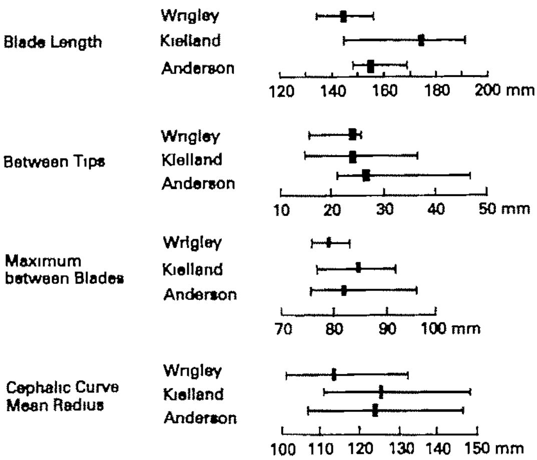

Fig. 2. Measurements of blades of forceps in use in Cardiff. Range ——— and Mean ■.

the Central Sterile Supplies Department. Each pair was engraved with a unique number to avoid duplication of measurements and it is believed that most forceps in circulation were measured, comprising 57 pairs of Wrigley forceps, 52 pairs of Kielland forceps and 57 pairs of Anderson forceps.

In addition three instrument makers gave us access to their specifications or master instruments. The latter were measured using the same technique.

Devices to allow accurate, rapid and reproducible measurement of both linear and radial detail were developed with the aid of the Bioengineering Department of the University Hospital of Wales (Gough *et al.* 1988).

Linear measurements

A perspex graduated plinth with two independent moving stops was used to determine overall length and the lengths of the components. The widths between the tips of the blades and maximum width between the blades were also measured.

Radial measurements

The mean radius of the cephalic curve of the blades was measured with a purpose designed instrument which has been described by Gough *et al.* (1988). The instrument comprises a depth gauge mounted in the centre of a platform which has locating pins to ensure accurate positioning of the forceps blade (Fig. 1).

Measurement of the pelvic curve of the blades was not undertaken since no accurate, reproducible method of measurement could be devised.

Results

The principal dimensions (mean, range and SD) of the three types of forceps studied are shown in Table 1. The essential dimensions of the blades in the three types are also shown in Fig. 2.

Wrigley's forceps

In his original description Wrigley does not give detailed measurements. In Table 1 it is seen that although the standard deviations for the blade measurements are less than for the other two types of forceps, for all the features of the blades there is a considerable range. Table 2 shows the features of the blades of Wrigley's forceps, comparing the Cardiff series with the measurements from two instrument makers' masters.

Kielland's forceps

Table 3 gives the blade data for Kielland's forceps, together with three instrument makers' master measurements and the dimensions shown in the drawings of the Original Kielland. An additional measurement of importance is the

Table 2. Measurements of Wrigley's forceps (in mm)

	Cardiff series (57 pairs)		Master instruments	
	Mean	(Range)	Maker A	Maker B (2 pairs)
Blade length	144	(137–157)	142	131, 134
Distance between tips	24	(16–28)	26	24, 23
Widest distance between blades	79	(76–83)	82	77, 79
Cephalic curve mean radius (left/right)	113	(101–132)	110/113	100/101 112/106

Table 3. Measurements of Kielland's forceps (in mm)

	Original pattern	Cardiff series (52 pairs)		Master instruments		
		Mean	(Range)	Maker A (2 pairs)	Maker B (3 pairs)	Maker C
Blade length	176	176	(146–192)	180,177	190, 190, 185	191
Distance between tips	15	24	(15–37)	25, 27	17, 17, 12	36
Widest distance between blades	80	85	(77–92)	89, 84	85, 87, 79	100
Cephalic curve mean radius (left/right)	126	125	(111–148)	130/127 126/137	114/117 142/134 130/127	
Distance between flat of shank and upper surface of blade (left/right)	8	—	—	8/6 6/7	6/6 14/16 7/11	8

vertical distance between the flat of the shank and the upper surface of the blade (Fig. 3), indicating the degree to which the pelvic curve has been set back.

Figure 3 shows a 'pair' of Kielland's forceps retrieved from the delivery unit after use in which the set of the blades is clearly different; the 'set back' being 8 mm and 16 mm respectively. In fact these blades, although numbered, had been mismatched during packing. Nevertheless, it is also evident that the design of the second blade is incorrect and does not conform to the Kielland pattern. None of the makers' patterns matched with the original dimensions. In particular, the maximum distance between the blades varied from 79 to 100 mm (recommended 80 mm) and the distance between the tips varied between 12 and 36 mm (recommended 15 mm). In two master pairs there was a major difference in the 'set back' of the blades.

Barnes/Anderson forceps

From the original descriptions, the blades of Anderson and Barnes forceps should be identical, the differences in design being confined to the shanks and handles. Table 4 and Fig. 4 compare the Cardiff observations on Anderson forceps with the findings of Forster (1971) in his study of Barnes forceps, the measurements obtained from manufacturers' master patterns, the measurements available from Anderson's original paper (see Hibbard 1988) and Rhodes (1960) preferred measurements.

Again, there are major variations in the important measurements. Figure 5 shows three pairs which clearly differ greatly in the configuration of the blades. It was subsequently discovered that the forceps on the left had been deliberately altered to increase the maximum distance between the blades to approximately those recommended by Rhodes. But the other two pairs, from different makers, also show clear differences. Not only are there wide variations, but also deviations from original descriptions—usually modifications for the better. The cephalic curve is of particular interest and importance. The shallow curve of the original designs (see Hibbard 1988) persists in the maker's master patterns but nearly all the

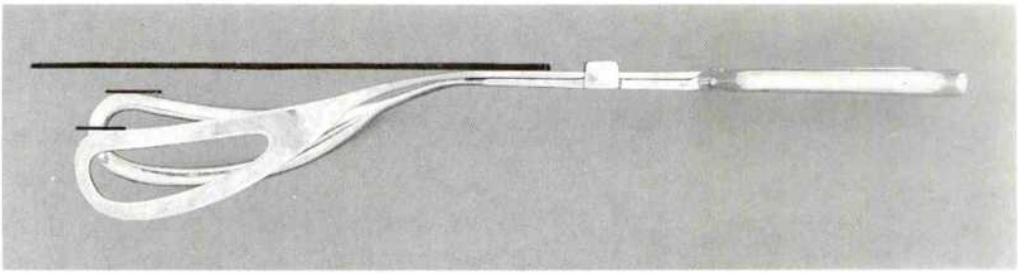

Fig. 3. Mismatched Kielland's forceps showing the differing set of the blades. The far blade has the correct set (8 mm from the plane of the upper surface of the shank).

Table 4. Measurements of Barnes/Anderson forceps (in mm)

	Original pattern	Cardiff series (57 pairs)		Forster*		Master instruments			
		Mean	(Range)	Mean	(Range)	Rhodes†	Maker A (2 pairs)	Maker B	Maker C
Blade length	171	154	(148–164)	171	(162–184)	160	157, 163	167	157
Distance between tips	16	27	(22–47)	25	(20–32)	30	29, 27	25	40
Widest distance between blades	78	82	(76–96)	86	(78–94)	90	89, 92	77	90
Cephalic curve mean radius (left/right)	—	125	(113–145)	—		112·5	142/141 121/128	151/145	137

*Forster (1971).

†Rhodes (1960) preferred measurements.

Cardiff instruments had radii below those measurements, although all were greater than Rhodes' recommendation. The distance between the tips also showed wide variations, which is clearly important in relation to the grip and main traction point of the forceps.

Discussion

The indications for applying forceps have changed considerably over the years. Until a century ago they were used infrequently and as a last resort. The primary consideration was to save the life of the mother, frequently at the expense of the baby. Labour might have been in progress for some days; during this time the baby's head would have become compressed and distorted but would still be high in the birth canal. Thus the forceps commonly used in the middle of the 19th century were long, to facilitate application when the head was high. The inner curve (cephalic curve) of the blades was shallow and the blades were relatively long to fit the elongated head. The blades were also relatively close together so that when they were closed they further compressed the baby's head to facilitate extraction through the narrowed birth passages.

In modern practice the indications for appli-

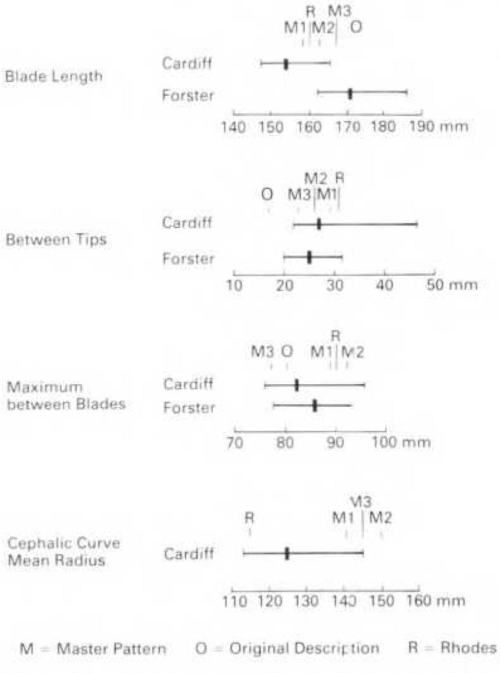

Fig. 4. Measurements of Anderson forceps compared with Forster's series of Barnes forceps, makers' master patterns and Anderson's original measurements. Range ——— and Mean ■.

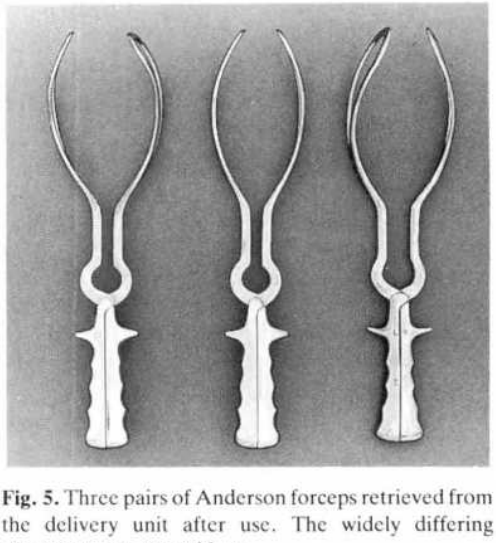

Fig. 5. Three pairs of Anderson forceps retrieved from the delivery unit after use. The widely differing measurements are evident.

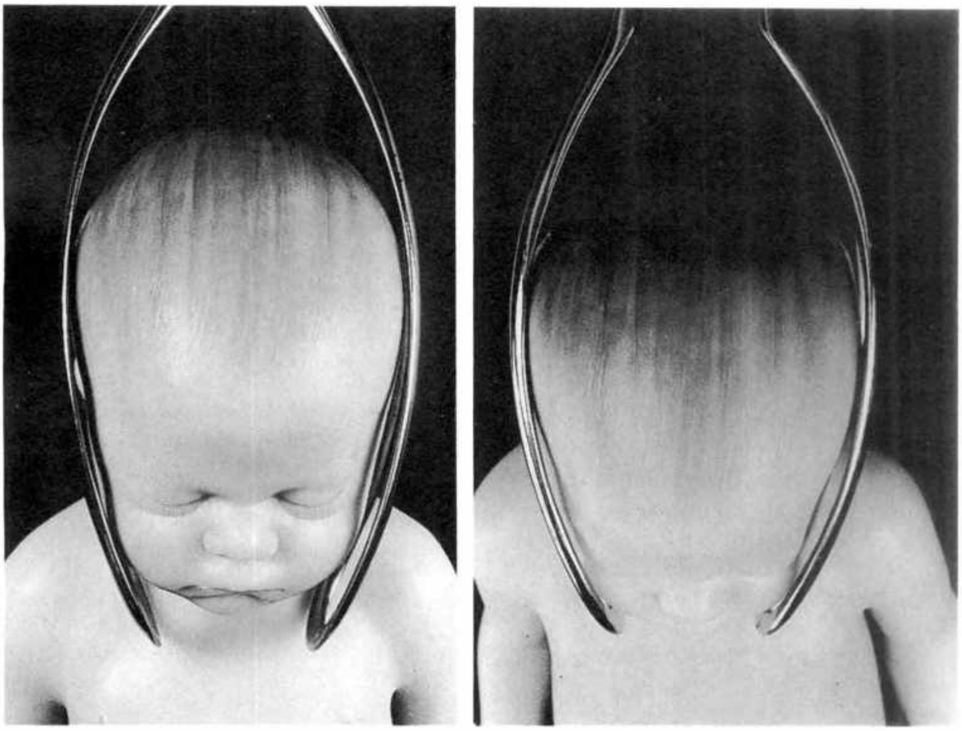

Fig. 6a **Fig. 6b**

Fig. 6. The cephalic fit of (a) Anderson's and (b) Wrigley's forceps.

cation of the forceps have changed. The primary consideration is now the wellbeing of the baby and compression of the baby's head is contraindicated. Long labours no longer occur and a severe degree of moulding of the head to facilitate its passage through the birth canal is rarely seen. The high forceps operation has been abandoned and replaced by caesarean section, so that forceps are now only applied when the head is lower in the birth canal.

The common designs of long forceps such as Barnes, Anderson and Simpson in current use have their origins in the mid 19th century. Although various modifications have crept in over the years, it is clear that their design is inappropriate to present needs. The present review, with detailed measurements, shows wide variations in their dimensions and there are apparent deficiencies in quality control, although distortion of some features may have occurred over decades of usage of individual pairs of instruments.

Other studies (Forster 1971, Morton 1973) have shown that measurements of forceps bearing the same name may differ widely, sufficient to be potentially dangerous in use. Even in designs of early 20th century origin considerable differences are found and this is well shown in the present review of Kielland's forceps, even though the measurements have been well defined and the design patented.

One of the few obstetricians of recent years to make a critical appraisal of forceps design for a specific community was Rhodes (1960). His preferred measurements, which have not been challenged subsequently, are shown in Table 4 and Fig. 4, where they are compared with Barnes Anderson forceps. Of particular note is his recommended cephalic curve of 112·5 mm radius, far less than the older types and approximating to the curve of the Wrigley forceps. Figure 6 shows that this is a more appropriate fit on the fetal head and, combined with the increased distance between the blades, results in appropriate distribution of forces, compared with the undue biparietal compression which is likely to occur with the older forceps.

There are few data available on cephalic measurements of contemporary newborn infants but an average ultrasonic biparieta measurement of about 95 mm at term is generally accepted. On this basis the potential for considerable compression of the fetal head with some of the current instruments is obvious, with a maximum distance between the blades being as little as 76 mm in some cases.

Since long forceps continue to be used, albeit inappropriately, and there appears to be relatively little resultant trauma it implies that operators do not use the potential mechanical advantage for compression provided by the long handles. However, this feature was of concern to Wrigley and is the reason for his rudimentary handles.

At the present time it is not clear what the ideal forceps measurements for a Caucasian population should be and this requires further investigation based on cephalometry. In the meantime obstetricians should be aware that rogue instruments with clearly unacceptable measurements may be in circulation. The potential for mismatching during cleaning and packing underlines the need for checking each pair of forceps before use.

There is a need for collaborative effort and commitment on the part of clinicians and instrument makers to provide tools specifically designed for present day needs which can be used with confidence and safety.

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'Normal but dead': perinatal mortality in non-malformed babies of birthweight 2·5 kg and over in the Northern Region in 1983

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Summary. The case notes relating to 75 of the 91 perinatal deaths of non-malformed babies of birthweight ≥2·5 kg born in the Northern Region in 1983 were examined. The major groups involved antepartum deaths of unknown cause (40%), and deaths due to intrapartum anoxia or trauma (35%). A case-control study compared each of the 75 cases with two controls matched for place of birth, obtained by taking the next two babies born in the same maternity unit (excluding perinatal deaths, birthweight <2·5 kg, and malformations). Four factors were found to be significantly associated with risk of perinatal death in this group: primigravidity, parity ≥3, not booked for antenatal care by 20 weeks, and corrected birthweight <3·2 kg (adjusted for gestation). Two further factors were related only to the risk of perinatal death consequent upon intrapartum events: labour post-term and malpresentation in labour. All four factors relevant to the whole group remained independently associated with risk of perinatal death after multivariate analysis by two techniques. Adjusted odds ratios (95% CI) were estimated as: primigravidity 2·1 (1·1 to 4·1); parity three or more 5·7 (1·9 to 17); not booked for antenatal care by 20 weeks 15·7 (3·0 to 81); and corrected birthweight <3·25 kg 2·5 (1·3 to 4·6). An avoidable factor, as defined, was detected in 50% of deaths. In 30% of deaths there was an avoidable factor (grade 2) such that absence may have been expected to lead to a different outcome had all other factors remained equal. Of the avoidable factors detected, 61% related to intrapartum management, as did 76% of the grade 2 factors. Most of these involved failure to respond to evidence of fetal distress in labour. The defined group constituted 21% of all perinatal deaths, suggesting that this is an important category, particularly as their potential for normal survival should otherwise have been high.

A collaborative survey of perinatal deaths has been in continuous operation in the Northern Regional Health Authority since 1980, under the auspices of a central co-ordinating group. Each consultant maternity unit throughout the region provides a local review group consisting of at least a midwife, a paediatrician and an obstetrician, one of whom acts as convenor. The convenor is notified of each perinatal death within the corresponding unit and any associated general practitioner obstetric unit. The local group is then responsible for enquiring into the

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associated circumstances and notifying in turn the central co-ordinating group via the Regional Medical Officer. The results of these routine enquiries are disseminated annually within the region, and have been the subject of a previous publication (Northern Regional Health Authority Co-ordinating Group 1984).

Each year, the central co-ordinating group has commissioned one or two more detailed supplementary studies into particular defined subsets of regional perinatal deaths. In 1983, a study was requested of perinatal deaths amongst non-malformed babies of birthweight ≥2·5 kg. These criteria were selected as encompassing a well-defined subgroup of perinatal deaths which were expected to show scope for prevention: they were encapsulated by the phrase 'normal but dead'. The aims of the study were threefold: to enumerate and characterize such deaths, to assess the role of pre-existing risk factors, and to examine the occurrence of avoidable factors in management.

The Northern Regional Health Authority covers an area with a total population of some three million people, and there are currently about 40 000 babies born in the region each year. There are 20 consultant obstetric units and six small independent general practitioner units. Previous regional survey data indicated about 500 expected perinatal deaths in 1983, with approximately 100 eligible for inclusion in the present study.

Subjects and methods

The study was a retrospective investigation of perinatal deaths of babies born within the Northern Region to residents of the region in 1983. Ascertainment of perinatal deaths was from notifications to the central co-ordinating group of the regional perinatal mortality survey. All such notification forms received which related to deaths in 1983 were scanned. Three groups were excluded from further consideration: babies of birthweight <2·5 kg, babies whose reported causes of death included a lethal congenital anomaly, and deaths occurring after the first week of life (notified as the regional survey is of extended perinatal mortality).

Notifications of eligible deaths were collected from each unit until a suitable batch had been assembled. A letter was then written to the local convenor seeking permission for one of us (W.K.) to visit the unit and abstract information from the clinical case notes on to a data collection form which had been agreed beforehand with the central group. If the attempt to arrange a visit was unsuccessful, a more detailed personal explanatory letter was written to the individual consultant concerned based on what had been learned of the reason for the failure, and a further attempt made to arrange a visit. Information was collected on the 36 variables covered by the routine regional notification form, including maternal demographic information, basic information on pregnancy, delivery and the infant, and details of outcome. To these were added four variables for four-digit ICD9 cause of death coding, 19 variables related to the course of pregnancy and labour in more detail, and 28 related to the neonatal course.

There were 39 350 births recorded in total in the Northern Region in 1983, and 470 were notified as deaths to the central co-ordinating committee. Of these, 42 proved to have suffered late neonatal death, leaving 428 true perinatal deaths, a perinatal mortality rate of 10·9 per thousand total births. The OPCS figure for perinatal mortality rate in the Northern Region in 1983 was 10·7 per thousand total births, a slight discrepancy largely due to differences in allocation to early and late neonatal deaths. At the same time the rate for England and Wales was estimated at 10·4 per thousand total births (OPCS 1984).

Of the 428 perinatal deaths notified to the regional survey, 92 were excluded from the present study because of lethal malformation and 245 were excluded with birthweights of <2·5 kg, leaving 91 (21%) eligible for further study. All attempts to arrange a visit to three units to collect details of 16 cases failed. This resulted in a final study group of 75 eligible cases, equivalent to a response rate of 82%.

Cause of death amongst the 75 cases was studied by consideration of Aberdeen classification (Baird *et al.* 1954), clinico-pathological classification (Bound *et al.* 1965), and four-digit four-way ICD9 coding (World Health Organization 1977). Despite this apparent complexity, the underlying causes fell readily into five major groups, shown in Table 1. The two largest groups, antepartum death of unknown cause (sometimes described as due to antepartum anoxia), and intrapartum events, together account for 75% of the deaths in this group of babies. The 26 deaths due to intrapartum events were divided evenly between those occurring

Table 1. Cause of death in 75 perinatal deaths of non-malformed babies of >2·5 kg, Northern region, 1983

Cause of death	*n*	(%)
Antepartum, cause unknown	30	(40)
Intrapartum events	26	(35)
Anoxia	20	(27)
Mechanical (vertex)	4	(5)
Mechanical (breech)	1	(1)
Mechanical (cord)	1	(1)
Antepartum haemorrhage	10	(13)
Placental abruption	9	(12)
Cause unknown	1	(1)
Miscellaneous fetal	5	(7)
Fetal blood loss	2	(3)
Sudden infant death syndrome	2	(3)
Infection	1	(1)
Miscellaneous pregnancy	4	(5)
Maternal diabetes	2	(3)
Pre-eclampsia/multiple	1	(1)
Rhesus isoimmunization	1	(1)

intrapartum and those postpartum; inspection of clinical records suggested that most of the latter babies were moribund at birth. The ascription of cause of death took full account of the findings in the 63 cases (84%) where necropsy had been carried out, but it may be that some of the remaining 12 had unsuspected major internal malformations (Gau 1977).

Assessment of the effect of pre-existing factors was by a case-control analysis. Two controls were used for each case, the next two deliveries in the intended place of delivery as the case which produced babies who weighed at least 2·5 kg, were not malformed, and did not end as perinatal deaths (Clarke *et al.* 1988). The distribution of each variable was inspected initially in case and control groups. Where these differed, formal statistical comparison was undertaken by analysis of the matched case-control triplets, using methods summarized by Kahn (1983). The odds ratio associated with the variable was estimated, together with the 95% confidence interval on this estimate. If the probability of obtaining the observed or a more extreme degree of departure from the expected value of unity under the null hypothesis was less than 5%, the odds ratio was taken as significant. If the variable proved to be a significant risk factor for perinatal death in this group, the corresponding population attributable risk was also derived (using the control frequency distribution as an estimate of the population frequency distribution).

When the variables significantly associated with perinatal death in this group of cases and controls had been identified, two further techniques were applied to estimate the adjusted odds ratios associated with each, independent of the other significant variables. The first method was a logistic regression analysis, based on a binomial distribution of outcomes with logit link function, fitted by an iterative maximum-likelihood method (Dobson 1983). The exponentiated coefficients of the fitted function were taken as estimators of the adjusted odds ratios, and were compared with those obtained from the second adjustment method applied, the Mantel–Haenszel technique (Mantel & Haenszel 1959).

Before commencement, the power of the study to detect various odds ratios as significantly different from unity was investigated. Since test power also depends on the frequency of occurrence of the factor in the control population, this was done over an assumed range of factor prevalences from 5% to 30%. The calculated power was derived from a notional unmatched significance test, and will therefore be a slight overestimate. The results are shown in Fig. 1. Power to detect odds ratios of ⩾3·0 was generally very satisfactory (>80%), and acceptable for odds ratios of 2·5 (>70%). At odds ratios of ⩽2·0, test power was generally less satisfactory, but odds ratios of <2·0 are usually regarded as denoting rather weak associations.

The final part of the study was the avoidable factor assessment. The definition adopted was initially based closely on that used by the Confidential Enquiry into Maternal Mortality (e.g. DHSS 1979): a 'departure from the accepted standards of satisfactory clinical and administrative care which may have played a part in the ensuing death'. Features not amenable to direct

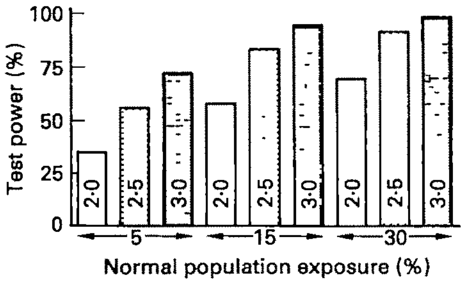

Fig. 1. Power of the tests used (see text for explanation).

clinical intervention, for instance maternal obesity, were excluded. The assessment was made jointly by the two writers, after an initial independent review of the completed forms. The assessment was made only on cases; we lacked the resources necessary to conduct fully blinded assessment of cases and controls. Only the events leading directly to death were considered, with no more than one avoidable factor assigned per case. No attempt was made to classify the ways in which accepted standards might be departed from in advance.

Consensus on avoidable factors was not always easy at first, so that a twofold classification was soon adopted which resolved the problem at once. This system divided the previous single overall rating of 'avoidable factor present', as in the Confidential Enquiry into Maternal Mortality, into a classification comprising grade 2 avoidable factors (absence may have led to a different outcome had all other features remained equal), and grade 1 avoidable factors (factor present but no direct link with death, or other adverse features present which may have led to death regardless of the avoidable factor). For example, if no action was taken over evidence of fetal distress in an otherwise unremarkable labour, and death subsequently occurred due to intrapartum anoxia, a grade 2 factor would have been ascribed. If, on the other hand, death had subsequently occurred due to mechanical factors during delivery, the factor would have been grade 1: although an avoidable factor was presented which probably contributed to the outcome, it could not be said that death would not have been expected if the fetal distress had been managed differently.

Table 2. Previous pregnancies in cases and controls

	Cases	Controls
Total pregnancies		
None	38 (51%)	65 (43%)
1–2	21 (28%)	70 (47%)
≥3	16 (21%)	15 (10%)
Total	75 (100%)	150 (100%)
Pregnancies 28+ weeks		
None	42 (56%)	75 (50%)
1–2	21 (28%)	68 (45%)
≥3	12 (16%)	7 (5%)
Total	75 (100%)	150 (100%)

Results

Case-control analysis

Several of the variables were suspected of association with perinatal death in this group of babies on the basis of previous published work, but showed little or no evidence of systematic difference between cases and controls in the present study. Maternal age, height, social class, and employment status were very similar in cases and controls. There was some tendency to excesses of single-parent mothers and non-married mothers amongst cases, but the differences failed to achieve significance at the 5% level. There was a slight (non-significant) excess of smokers amongst control women. Abnormal findings during antenatal care (including hypertension, proteinuria, ultrasound findings suggestive of abnormality or disordered growth, and abnormal biochemical tests of placental function) were distributed similarly in cases and controls. There was a slight excess of threatened miscarriage in the present pregnancy in cases (8% against 5% of controls), but again this difference failed to achieve significance at the 5% level. There was no difference in previous fetal losses.

Number of previous pregnancies differed between cases and controls (Table 2), with excess amongst cases of first-ever pregnancies and of parity three or more. The odds ratio associated with primigravidity over gravidity two or three was 2·4, with 95% CI 1·1 to 5·1. The probability of obtaining this or greater deviation in either direction from a true underlying odds ratio of unity is 0·03 ($P = 0{\cdot}03$), and the null hypothesis was therefore rejected at the 5% level. The odds ratio associated with a parity of ≥ three was 5·5 (95% CI 1·0 to 31·4). The null hypothesis was (just) rejected at the 5% level.

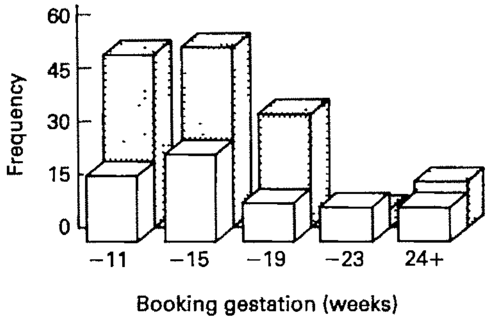

Fig. 2. Distribution of gestational age at booking. □, Cases ($n = 75$); □, controls ($n = 150$).

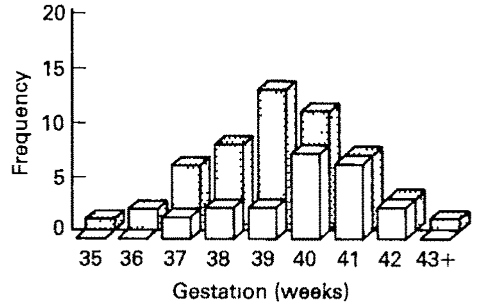

Fig. 3. Distribution of gestational age at delivery (deaths due to intrapartum events). ☐, Cases ($n = 26$); ☐, controls ($n = 52$)

Figure 2 shows the distribution of gestation at booking for antenatal care amongst cases and controls. This was measured as completed weeks of pregnancy based on the estimate of the local assessor determined from the clinical history, repeated examination, and often ultrasound. The excess of women unbooked by 20 weeks was associated with an odds ratio of 2·5 (95% CI 1·3 to 4·8, $P = 0{\cdot}009$).

There was a marked preponderance of cases with shorter gestation at birth compared with controls in those cases where death occurred antepartum. This is of course unsurprising, since in most cases such antepartum fetal death was closely followed by either spontaneous or induced labour. However, when the analysis was restricted to the 26 cases where intrapartum or neonatal death was due to intrapartum events, there was a clear excess of deliveries at 40 weeks gestation or more compared with the 52 associated controls (Fig. 3). The matched case-control triplet analysis estimated the associated odds ratio as 3·3 (95% CI 1·2 to 9·4, $P = 0{\cdot}02$).

Since presentation in labour was clearly irrelevant to cases where fetal death had occurred antepartum, consideration of the possible associations of this variable were similarly restricted to the 26 cases with intrapartum or neonatal deaths due to intrapartum events and their 52 associated controls. Table 3 shows the excess of malpresentations amongst the cases. The matched case-control triplet analysis estimated the associated odds ratio at 8·0 (95% CI 1·3 to 50·4, $P = 0{\cdot}03$).

The possible associations of disordered fetal growth, as assessed by birthweight, were examined in all 75 cases and 150 controls. A confounding factor, however, was clearly gestation at delivery which differed between cases and controls. The confounding effects of gestation were corrected for, by deriving the linear regression of birthweight on gestation for all controls and calculating the expected weight at term for each individual from the the regression coefficient. The distributions of corrected birthweights amongst cases and controls demonstrated a marked tendency towards lower birthweights amongst the cases. The excess of cases at <3·25 kg corrected birthweight was associated with an odds ratio of 3·2 (95% CI 1·7 to 6·7, $P = 0{\cdot}001$).

Table 4 summarizes the risk factors associated with raised odds ratios of perinatal deaths of non-malformed babies of ≥2·5 kg. The final column shows the population attributable risk, that is the proportion of this type of perinatal death which is associated with each risk factor.

Two methods were used to adjust the odds ratios for possible confounding effects. Firstly, a logistic regression was fitted, using all cases and controls with the four significant independent factors for all deaths (primigravidity, parity ≥3, unbooked by 20 weeks, and corrected birthweight <3·2 kg, together with a constant term. The estimated regression fitted the data well (deviance 2·88, d.f. 6, fit 0·82). When any single independent factor was omitted, the fit worsened significantly, so the full model was accepted. The exponentiated fitted coefficients may then be taken as estimates of the adjusted odds ratios, which are shown with their 95% CI in Table 5. The adjusted odds ratio associated with not booking by 20 weeks has risen markedly in comparison with its unadjusted counterpart, at the expense of slight reductions in the adjusted odds ratios of both primigravidity and low corrected birthweight.

When attention was turned to the two remaining variables, those related to intrapartum events, there were problems with the analysis. Malpresentation and late booking proved to be perfectly correlated in these data, so the full model was indeterminate. The model omitting

Table 3. Presentation in labour in cases and controls, deaths due to intrapartum events only

	Cases	Controls
Presentation		
Vertex	22 (85%)	51 (98%)
Other cephalic	2 (8%)	0 (—)
Breech	2 (8%)	1 (2%)
Total	26 (100%)	52 (100%)

Table 4. Odds ratios of significant associations

Associated factor	Odds ratio	95% CI	Population attributable risk (%)
Primigravidity	2·4	1·1 to 5·1	40
Parity ≥3	5·5	1·0 to 31·4	20
Booked ≥20 weeks	2·5	1·3 to 4·8	15
Corrected birthweight <3250 g	3·2	1·7 to 6·7	50
Labour post-term*	3·3	1·2 to 9·4	50 (15)
Malpresentation*	8·0	1·3 to 50·4	10 (5)

* Calculation based on deaths due to intrapartum events only. (Attributable risk based on whole group parenthesized.)

one of these terms fitted the data only moderately (deviance 13·8, d.f. 10, fit 0·18), and the reduced model omitting labour post-term did not result in a significantly worse fit. The effects of these two variables were therefore omitted when considering adjusted odds ratios.

The second adjustment method, the Mantel–Haenszel technique, was also applied to the data to compare the resulting adjusted odds ratios. There was excellent agreement with the multiple logistic model, the largest difference being between odds ratios of 5·7 and 5·3 for the effects of parity ≥3, a discrepancy of only 7%.

Avoidable factor assessment

An avoidable factor, as defined, was assessed as present in a total of 38 (50%) of the 75 deaths. In 16 cases (20%) the avoidable factor was assessed as grade 1 (factor not definitely linked with death), but in 22 cases (30%) the avoidable factor was assessed as the more definite grade 2 (absence may have been associated with a different outcome). The proportion of deaths showing an avoidable factor differed markedly according to the time of death relative to labour, being only 8 of 39 antepartum deaths (21%), but 15 of 16 intrapartum deaths (94%), and 15 of 20 postpartum deaths (75%).

The nature of the avoidable factors discovered is detailed in Table 6. Efforts were made to keep avoidable factor assessment as clearcut as possible. Delay in acting on evidence of antenatal problems was not recorded as excessive unless >2 weeks (including two clinic visits or inpatient admission). Evidence of problems not responded to included substantial persistent weight loss and persistently reported marked diminution of fetal movements. Where avoidable factors related to a lack of readable continuous fetal heart monitoring in labour despite indications, the indications to monitor comprised either a fetus at risk on the basis of abnormal antenatal history and findings, or the induction of labour because of detected abnormal progress of the pregnancy. (All five of the relevant case notes contained a record that either the fetus was regarded as at high risk or that labour was being induced because of fetal well-being; in three cases the concern related to persistent hypertension and in two to placental function.)

Excess delay in responding to markedly abnormal fetal heart records in labour involved failure to respond within 2 h. A response was taken as any evidence that the situation had been reassessed by whatever means were available on the spot; in particular the assessors never regarded a failure to apply a specialized technique like fetal blood sampling as constituting an avoidable factor. The abnormal fetal heart records in this and the next group (complete failure to respond to abnormal fetal heart record) always included either late decelerations or other decelerations occurring together with one of more baseline abnormalities (bradycardia, tachycardia or diminished variability). Changes within 1 h of death were excluded as agonal phenomena, and changes which subsequently resolved were excluded as transient. Further factors involved traumatic delivery (judged from

Table 5. Adjusted odds ratios of significant associations

Associated factor	Odds ratio	95% CI
Primigravidity	2·1	1·1 to 4·1
Parity ≥3	5·7	1·9 to 16·9
Booked ≥20 weeks	15·7	3·0 to 81·0
Corrected birthweight <3250 g	2·5	1·3 to 4·6

Adjustment by multiple logistic regression using five-parameter model (including constant term) for all cases and controls.

Table 6. Classification of 38 avoidable factors found in 75 perinatal deaths of non-malformed babies of ≥2·5 kg, Northern region, 1983

Avoidable factor	Grade 1	Grade 2	Total
Excess delay acting on evidence of antenatal problem	8	2	10
Unmonitored, or unreadable trace, despite clear indications	2	3	5
Excess delay acting on fetal distress in labour	2	1	3
No action on fetal distress in labour	2	8	10
Traumatic delivery	1	4	5
Concealed complicated delivery	1	3	4
Delayed neonatal management	0	1	1
Total	16	22	38

the combination of ascribed cause of death and the delivery record), concealed delivery with malpresentation, and delayed neonatal management (>1 day).

Of the total of 38 deaths associated with an avoidable factor, no less than 23 factors (61%) related to intrapartum management, and 18 (47%) related to monitoring in labour. Of the total of 22 deaths associated with a grade 2 avoidable factor (absence of which may have been expected to lead to a different outcome), 19 (86%) related to intrapartum management.

Discussion

Reliability and validity

Ascertainment of perinatal deaths in the Northern Region by notification to the central co-ordinating group is known to be virtually complete (Northern Regional Health Authority Co-ordinating Group 1984). The only significant source of incompleteness in this study is therefore the failure of access to the case notes of 16 of 91 eligible cases from three of the 26 units. Although this response rate of 82% appears fairly substantial, it is not possible to infer whether those units to which access was not obtained were systematically different in outlook and practice from the co-operating units. Although the causes and circumstances of death given on the notification forms to the central co-ordinating group did not differ systematically between the responding and non-responding units, it was impossible to compare the two groups in any more formal way since there often proved to be substantially more information extracted from clinical records than that summarized on the notification forms (which were designed for a different purpose). The 18% non-responses must therefore remain as a possible source of bias in the results; it seems unlikely, however, that this mechanism would lead to an overestimation of the preventable deaths, or that differences in exposure to pre-existing risk factors would be large. In general, the distributions of variables in the control group were close to those expected from previous studies, which should increase confidence in the validity of the present study.

Scope of the problem

Perinatal mortality rates in Britain have been falling more or less steadily since the mid-1930s, when the level for England and Wales was about 60 per thousand total births, to a level of about 10 per thousand total births now. Within this remarkable decline, however, there remain substantial regional variations: in 1983 the range of regional rates in England encompassed 8·6 and 12·3 deaths per thousand total births, a variation of 35% of the national rate. For the 3-year period 1982–84 within the Northern Region, perinatal mortality rates for the 16 district health authorities varied from 8·5 to 13·9 per thousand total births, a variation of almost 50% of the regional rate. Although some of this variation is attributable to population differences, principally of deprivation, some is clearly not (Mallet & Knox 1979). Some of the residual variation may be related (although not simply) to the effectiveness of health care delivery in pregnancy, labour and the puerperium (Knox *et al.* 1980).

By restricting the present study group to non-malformed babies of at least 2·5 kg birthweight, we were able to focus attention on a group who were apparently well equipped to survive, but did not. This group might therefore be expected to accumulate more deaths associated with preventable factors, which may mean little if the target group had been so restrictively defined as to be very small. This 'normal but dead' group, however, accounted for 21% of the perinatal deaths in the Northern Region over the study period, a not insubstantial proportion. There is no reason to suppose that the Northern Region is unusual in this respect, nor that obstetric care differs systematically from the rest of the country.

The concept of avoidability

Recognizing that this is a subject likely to arouse controversy, we followed a well-established precedent, the Confidential Enquiries into Maternal Mortality (e.g. DHSS 1979), as closely as possible. The recognition that there has been 'a departure from the accepted standards of satisfactory clinical and administrative care which may have played a part in the ensuing death' requires, of course, that there are accepted standards against which to assess. In the absence of a set of predefined standards to cover the full variety of clinical situations, there must remain an element of individual judgement in avoidable factor assessment.

Contrasting views have previously been expressed about the effect of this on the reliability of study findings. On the one hand, it is suggested that assessment of avoidable factors is so subjective as to be worthless and may decrease response rates (Northern Regional Health Authority Co-ordinating Group 1984; Macfarlane 1984), while on the other hand the concept has been found to be useful (MacVicar 1980; Mersey Regional Working Party on Perinatal Mortality 1982). Having taken the decision to include this assessment, the writers attempted to improve reliability by three strategies. Firstly, we adopted as clearcut and rigorous criteria of avoidability as we were able, restricted to the area of clinical intervention. Secondly, we reviewed the information extracted from the case notes both independently and subsequently in conjunction. Thirdly, in order to improve comparability between the assessors, the subdivision into two grades of avoidable factor was accepted. Following this, agreement between the assessors was easy and universal. This was felt to be the optimum possible short of a blind case-control review, which was impracticable given the resources available.

It should be stressed that the end result of this approach is to make the avoidable factors, whether grade 1 or 2, described in the present study more restricted, and we believe more clearcut, than in other reports. For example, the Mersey Regional study (Mersey Regional Working Party on Perinatal Mortality 1982) was apparently based on much more wide-ranging avoidable factors, including for instance 'unsupported mother', 'severe psychiatric problem' and 'excessive obesity'. None of these would have been included even as grade 1 factors in the present study, which restricted avoidable factors to those related to single defined episodes of management or care which could have been handled differently in the situation.

No attempt has been made in the present study to enquire into the circumstances which might have underlain occurrences of avoidable factors. These might have included difficulties related to provision of physical resources or staff, or to inefficiencies in the organization of care. Although it must be said that the great majority of avoidable factors were related to the application of fairly basic principles of care, the local investigation of any underlying features would be a logical next step.

Present and previous findings

The high proportion of deaths due to intrapartum events has not been highlighted by previous work. There is evidence to suggest that causes of all perinatal deaths in the Northern Region are not systematically different from the rest of the country (Northern Regional Health Authority Co-ordinating Group 1984), and so there is no reason to suppose a major difference in this subgroup of perinatal deaths. Part of the explanation may be that non-malformed babies weighing ≥ 2.5 kg have not been considered as a separate group before, and their causes of death therefore do not stand out from the greater numbers of babies dying through immaturity and malformation. Additionally, there was a clear tendency for babies dying of intrapartum anoxia to be certified as neonatal deaths rather than stillbirths, which may obscure the mechanism of death; in many cases in this study there was retrospective evidence that the baby had died *in utero,* but of course strenuous resuscitative efforts were made after delivery in accordance with the benefit of doubt, and death was typically certified as occurring after some brief period of extrauterine 'existence'. For all practical purposes, however, these were clearly deaths due to intrapartum disasters.

Several factors were not found to be associated with perinatal death in this group, although they may have been suspected on the basis of previous evidence (Morris & Heady 1955*a*, 1955*b*; Heady *et al.* 1955*a*, 1955*b*; Daly *et al.* 1955; Butler & Bonham 1963; Butler & Alberman 1969; Chamberlain *et al.* 1975, 1978; OPCS 1983). Principal amongst these were maternal age, height, social class and marital status; previous fetal loss, maternal disease and smoking; and antenatal abnormalities. Several reasons may be suggested for the non-appearance of these suspected associations in the present study.

Firstly, the power of the study may have simply been insufficient to have a reasonable chance of detecting a true risk factor. This question has already been addressed, and the conclusion drawn that the study design carried substantial power to detect true odds ratios of at least 2·0 unless occurrence of the factor was uncommon in the population. This potential underestimation of a true effect is not likely to apply to variables reasonably evenly distributed in the childbearing population, such as age, height, social class and smoking. On the other hand, it is quite likely that the study simply failed to detect a fairly substantial true association with rare events such as previous late fetal losses, pre-existing maternal disease, and antenatal abnormalities.

The second mechanism whereby previously described risk factors may not appear involves the selection of cases for study. Restriction of cases to normal-birthweight non-malformed babies may have suppressed the effect of factors mediated largely by effects on fetal growth or development. This mechanism almost certainly explains the initially surprising lack of relation with maternal cigarette smoking in this study. The harmful effects of cigarette smoking on the fetus appear likely to be mediated by disturbance of intrauterine growth, perhaps interacting with maternal nutrition (Rush & Cassano 1983). The present study provides some support for this mechanism. It is probable that several other well-established risk factors for overall perinatal death also do not apply to this group because their association occurs through low birthweight, including maternal height, social class, marital status, and perhaps age.

The third reason for non-appearance of previously documented risk factors for perinatal death may actually relate to the general recognition of such factors by clinicians. Intervention in pregnancies considered to be a high risk, in the form of elective operative delivery or induction of labour with a greater readiness to terminate labour operatively or instrumentally, could actually abolish the former effect of such factors. A report from the USA (Freeman *et al.* 1985) confirms this mechanism, showing that there was no increased risk of perinatal death in pregnancies following a stillbirth, but that intervention in such pregnancies was very much more common. As well as previous fetal losses, this mechanism may also apply to pre-existing maternal disease and antenatal abnormalities.

One of the few comparable perinatal death investigations to consider avoidable factors explicitly was the Mersey Regional study (Mersey Regional Working Party on Perinatal Mortality 1982), which reported 60% of perinatal deaths to be associated with avoidable factors. As discussed above, their definitions were clearly more wide ranging, and it is notable that 74% were deemed to be inevitable, suggesting comparability between their 26% 'non-inevitable' deaths and the present 30% with grade 2 avoidable factors. The Mersey study also found the proportion of cases with an avoidable factor to be higher in the group of normal-birthweight non-malformed babies. This group may be expected to demonstrate a higher proportion of preventable deaths (McIlwaine *et al.* 1979), being freed from the large numbers of inevitable deaths of grossly immature and severely malformed babies. This observation may also account for the rather lower proportion of avoidable factors detected (MacVicar 1980) in the Leicester survey of all perinatal deaths (20%, half of which were related to antenatal care).

Many of the avoidable factors detected related to the detection of probable fetal distress by intrapartum monitoring. This is certainly not to deny the problems with these techniques, principally the high false-positive rates arising from difficulties in interpreting many changes. The present results, however, apply to clearly defined and marked abnormalities, all of which arose at least 3 h before death and did not resolve or remit. The application of continuous monitoring as a routine in all labours remains at best controversial and is often unwanted by women in labour (MacDonald *et al.* 1985; Kelso *et al.* 1978; Curzen *et al.* 1984; Niswander *et al.* 1984). When, however, there is prior evidence of substantial risk of fetal distress in labour, these results imply that there are considerable potential benefits to the appropriate application of the technique.

Detected risk factors

Four characteristics emerged as associated significantly with the studied subgroup of perinatal deaths, and remained so after adjustment for confounding (although the magnitudes of the associations were modified). These characteristics may be summarized as late booking for antenatal care, a tendency to low birthweight, primigravidity, and parity three or more. An additional two characteristics were associated with a further subgrouping of perinatal deaths, those due to intrapartum causes (principally anoxia). These characteristics were labour occurring post-term, and fetal malpresentation in labour.

Of course, association does not imply causation. On reviewing the records of all cases unbooked by 20 weeks, not one could be found in which the notion could be supported that the ensuing death might have been avoided by an earlier visit to an antenatal clinic. The conclusion must not be the simplistic one that early booking could prevent any of the deaths, but rather that late booking is acting as a marker variable serving as a proxy for one or more underlying risk factors. The nature of the underlying problem remains undefined, but in view of the known associations of late booking the most profitable area of search is likely to be in the ways that social disadvantage and deprivation continue to affect perinatal health (Chalmers 1985).

The occurrence of an association with lower than expected birthweight despite restriction of the study group to those of $\geq 2{\cdot}5$ kg is interesting, suggesting as it does a link with disordered fetal growth even within the restricted group. It may be that the underlying cause of death in some cases acts first on intrauterine growth, or equally that some causes of death act preferentially on those already at risk because of disordered growth. It is also impossible to exclude an effect of post-mortem weight loss *in utero*, but this is thought to be small because of the short delays between fetal death and delivery.

The effects of both primigravidity and high parity have been described many times before, but there has been disagreement recently on the possible mechanism and on the best way to describe the data (Roman *et al.* 1978; Bakketeig & Hoffman 1979; Golding *et al.* 1983; Chamberlain 1979). Proponents of the longitudinal approach suggest that there is a major selection effect acting to make high-parity pregnancies appear spuriously at-risk because women with previous fetal losses are more likely to embark on further pregnancies; on the other hand, proponents of the cross-sectional approach claim that their simpler method of analysis gives a better description of underlying risks after all. It may be interesting to note that the association with high parity in the present study acted independently of any effect of previous fetal losses. The associations with both primigravidity and high parity were both reduced slightly by adjustment for the effects of late booking and low birthweight, but remained significant, confirming effects independent of these confounding variables as well.

The existence of an association between malpresentation and perinatal death due to intrapartum events is not unexpected. The finding was based on a few cases with malpresentation only, and the magnitude of the effect may therefore be overestimated (Chalmers 1983). These cases were split evenly between those in which the malpresentation had been diagnosed correctly from the outset but complicated management of fetal distress, and those related to traumatic factors associated with delay in establishing the presentation. The association between labour at or after term and death due to intrapartum factors is also not unexpected on theoretical grounds, although a previous study suggested that this factor was no longer important (McIlwaine *et al.* 1979). The same group of investigators had previously postulated that this was because of increased resort to induction of labour (McNay *et al.* 1977), but this was only on the grounds of coincident secular trends, and has been dismissed by more rigorous studies (Chalmers *et al.* 1976; Newcombe & Chalmers 1977; Chalmers *et al.* 1978). In view of the potential hazards and unacceptability of the frequent use of induction of labour it would certainly appear inappropriate to suggest increased resort to this technique as a preventive measure, and there is recent evidence that such a policy would not alter perinatal outcome (Cardozo *et al.* 1986).

Implications

When the pre-existing factors were analysed by multivariate methods to account for the possibility of confounding amongst the variables detected as associated with risk of perinatal death in this group, the associations remained significant for the four variables detected in the whole group of deaths. This strengthens the evidence in favour of their acceptance as true associations, as does the good agreement between the two methods of adjustment. These associations, however, appear to be unlikely candidates as causative factors. It would appear more reasonable to regard them as markers to increased degrees of risk of occurrence of this type of perinatal death, in non-malformed babies of normal birthweight.

It must be stressed that these cases have been compared against the highest possible standards of care; however, the occurrence of a substantial proportion of avoidable factors amongst them suggests scope for improvement in management. We have not sought to unravel the perhaps complex circumstances underlying the occurrence of avoidable factors, and it is clearly impossible to imagine reducing their incidence to absolute zero. The aim, however, must surely be to approach this as closely as is possible. If for example it were theoretically possible to attain this for the grade 2 avoidable factors, the potential effects would extend to 7% of all perinatal deaths, or about 400 in England and Wales in 1983.

The grade 2 avoidable factors reported here relate exclusively to the application of known standards of care to the management of mostly already demonstrably abnormal pregnancies. The great majority of factors occur clustered strongly around the management of labour and delivery in women with such pregnancies. To accomplish a reduction in these avoidable factors would therefore not require the application of new methods or technology, nor the imposition of unwanted interventions in large numbers of women with normal pregnancies. Before obstetricians consider any more such steps, it may be prudent to consider whether the sort of avoidable factors described here have yet been restricted to an irreducible minimum level.

The auditing of perinatal care on a more systematic basis would be a major way to encourage this process. It is suggested that the identification of the subgroup of perinatal deaths occurring in non-malformed babies of birthweight $\geq 2{\cdot}5$ kg would form a logical starting point. These babies are apparently well equipped to survive until the terminal event ('normal but dead'), and on the basis of this study there is likely to be a high degree of avoidability to their deaths. The exclusion of groups of perinatal deaths which are unlikely to be preventable would permit the deployment of a confidential enquiry approach in an efficient and logical way

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Treatment with GnRH agonists before myomectomy and the risk of short-term myoma recurrence

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Summary. Twenty-four women with symptomatic multiple uterine myomas were allocated randomly to treatment with buserelin, 1200μg/day intranasally, for 3 months followed by myomectomy ($n = 8$) or to immediate myomectomy ($n = 16$). Pre-operative treatment with buserelin reduced the mean uterine volume from 432 (SD 165) to 242 (SD 82) ml ($P < 0{\cdot}01$) but intra-operative blood loss and postoperative morbidity were not significantly less in this group. Six months after operation, pelvic examination was normal in all the patients. However, ultrasonography with transvaginal probe demonstrated the presence of myomas of <1·5 cm in five women (63%) treated pre-operatively with the analogue and in two women (13%) who underwent immediate surgery ($P < 0{\cdot}05$). Induction of a period of hypo-oestrogenism before myomectomy seems to favour short-term recurrence of uterine myomas, limiting the efficacy of surgery.

GnRH agonists have been shown to be effective in reducing the volume of uterine leiomyomas (Healy *et al.* 1986; West *et al.* 1987; Friedman *et al.* 1988). Some authors have suggested the pre-operative use of these drugs with the aim of facilitating myomectomy and decreasing postoperative morbidity in conservative and definitive surgery for myomas (Maheux *et al.* 1987; Kessel *et al.* 1988; Andreyko *et al.* 1988), but no controlled trials have yet been published.

To analyse the benefit of pre-operative GnRH treatment in women undergoing myomectomy we designed a randomized clinical trial comparing buserelin with no pre-operative treatment. The aim of the study was to assess the effect of buserelin treatment on intra-operative blood loss, postoperative morbidity and short-term myoma recurrence after surgery.

Subjects and methods

Twenty-four women (mean age 33·6 years, range 24–38) with symptomatic multiple uterine leiomyomas, attending the gynaecology outpatient clinic of our institutions, entered the study. The prevalent symptom was infertility in 18 and menorrhagia in six. The diagnosis was made by pelvic exploration and transabdominal and transvaginal ultrasonography. Since the frequency of ultrasound myoma recurrence after myomectomy is unknown, we designed an asymmetric 1:2 randomized trial, with the aim of obtaining quickly information on the frequency of recurrence without preoperative treatment. Using a randomization list the patients were allocated in a 1:2 ratio to treatment with intranasal buserelin, 1200 μg/day, for 3 months followed by myomectomy (buserelin group, 8 subjects) or to an immediate conservative oper-

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Table 1. Clinical and ultrasonographical (US) data of the patients.

Patients	Main symptom	Pretreatment uterine volume (ml)	Myomas removed at surgery	Findings at 6 months follow-up	
				Uterine volume (ml)	Myomas
Buserelin					
1	Infertility	321	4	102	–
4	Infertility	465	5	121	1
6	Menorrhagia	392	2	98	1
11	Infertility	249	2	101	–
14	Infertility	627	8	131	1
15	Infertility	713	10	112	1
20	Infertility	423	2	95	1
23	Menorrhagia	270	2	89	–
Mean (SD)		432·5 (165·5)		106·1 (14·1)	5 (63%)
Control					
2	Infertility	435	2	108	–
3	Infertility	659	2	121	–
5	Menorrhagia	412	4	96	–
7	Infertility	548	8	116	1
8	Menorrhagia	324	2	121	–
9	Menorrhagia	429	2	132	–
10	Infertility	398	3	121	–
12	Infertility	645	7	135	–
13	Infertility	276	2	94	–
16	Infertility	485	2	115	–
17	Infertility	423	4	119	–
18	Menorrhagia	638	6	127	–
19	Infertility	387	2	105	–
21	Infertility	512	6	127	–
22	Infertility	756	16	132	1
24	Infertility	445	4	89	–
Mean (SD)		485·8 (131·8)		116·1 (14·1)	2 (13%)

ation (control group, 16 subjects). The clinical characteristics of the patients and ultrasound findings are reported in Table 1. Serum 17-beta-oestradiol levels were measured monthly to monitor ovarian suppression during buserelin therapy. The myomectomies were performed as recommended by Buttram & Reiter (1981) and were always done by the same team. The duration of operation, intra-operative blood loss, and postoperative febrile morbidity were recorded. The postoperative follow-up included pelvic exploration at 3 and 6 months after the operation, and a transabdominal and transvaginal ultrasound examination at the latter time. The patients were asked to avoid pregnancy until the first follow-up examination. The total uterine volume and that of each identifiable myoma were calculated by measuring the three largest diameters (D) (lengthwise, transverse and anteroposterior) and applying the formula used for the volume of an ellipsoid: $D1 \times D2 \times D3 \times 0{\cdot}5233$. These measurements were performed during the diagnostic and postoperative ultrasonographies in all the patients by a physician unaware of the patient's group allocation and during myomectomy in those treated with buserelin. For statistical analysis Student's t and Fisher's tests were used.

Results

The pre-operative buserelin treatment was completed in all patients and no severe side effects were observed. Amenorrhoea was established in all the women within 6 weeks of the start of treatment. The mean serum 17-β-oestradiol level fell from 168 (SD 76) pg/ml to 28 (SD 12) pg/ml after 3 months of treatment. With the administration of buserelin the mean uterine volume was reduced from 432 (SD 165) to 242 (SD 83) ml ($P < 0{\cdot}01$). A conservative operation was performed in all the patients. The mean duration of the operation was 98 min (range 80–127) in the buserelin group and 92 min (range 83–124) in the control group. The mean number of myomas removed was 4·3 (SD 3·1) in the buserelin group and 4·5 (SD 3·9) in the control group, and there was a mean blood loss of 235 (SEM 22) ml and 275 (SEM 35) ml respectively (difference in means = 40 ml, SE = 41). None of these differences was statistically significant.

Postoperatively, two women of the buserelin group and three in control group developed pyrexia of not over 39°C, which responded to antibiotic treatment within 4 days.

The clinical examination at 3 months was negative in all the women. One in the control group conceived during the fourth month of follow-up. Pelvic exploration at 6 months did not reveal anomalies in any patient of either group. However, at ultrasonography myoma recurrence was observed in five women (63%) of the buserelin group and in two (13%) of the control group ($P < 0{\cdot}05$) (Table 1).

Discussion

Recently the results of a controlled randomized study suggested that pre-operative treatment with GnRH agonists may decrease the blood loss and postoperative febrile morbidity in women undergoing hysterectomy for uterine myomas (Lumsden *et al.* 1987). Equivalent studies on conservative surgery for uterine myomas are lacking, but it is widely believed that GnRH agonists may facilitate myomectomy by reducing the volume of the myomas and vascularization of the uterus (Maheux *et al.* 1987; Andreyko *et al.* 1988). Our results did not demonstrate that any advantage was gained by pre-operative administration of intranasal buserelin. The duration of the operation, intra-operative blood loss and postoperative febrile morbidity in the buserelin-treated group were similar to those in the controls. Unfortunately our study did not include a laparoscopic follow-up, which could have revealed any favourable effect of pre-operative therapy in terms of post-surgical adhesions.

The ultrasound examination performed 6 months after surgery demonstrated a greater frequency of recurrence in the short term in the women treated with buserelin. These myomas were intramural in all cases and <1·5 cm in diameter. They were missed at pelvic exploration, and not associated with a recurrence of symptoms. The use of a transvaginal probe was essential for their diagnosis; otherwise they would have been difficult to identify with abdominal ultrasonography alone.

The greatest limitation of our study is the small sample size, but it was designed as a pilot study to identify clinically important differences in the duration of operation, intraoperative blood loss, and possibility of myoma recurrence in the short term. In any case, the sample size was sufficient to reveal an increase in the frequency of recurrence from 10% in the control group to 70% in the treated one.

Patients in the buserelin group were examined 9 months after randomization compared with 6 months for the immediate operation group We consider, however, that this difference is not important since ovarian activity was suppressed in the buserelin treated women during the three additional months, and in any case the main aim of the study was to assess the myoma recurrence rate 6 months after myomectomy.

The greater frequency of rapid myoma recurrence in the patients treated preoperatively with buserelin is in all probability attributable to the decrease in volume and consistency of the myomas induced by the analogue, making the smaller tumours no longer identifiable during operation. A careful ultrasound examination at the end of the medical treatment before surgery would possibly have helped the surgeon, providing a precise 'map' of smaller lesions. However, this requires clinical confirmation. Furthermore, a careful clinical follow-up is necessary to clarify the significance of the minimal tumours revealed by follow-up ultrasonography in our study. The natural history of uterine myomas is not well known and we do not have sufficient elements to predict if and when a small myoma will produce clinical symptoms.

In summary, despite the small size of our series, our study indicates the need for a careful assessment of the possibly greater frequency of short-term recurrence of uterine myomas in patients receiving GnRH agonists before surgery, as already suggested by other authors (Kessel *et al.* 1988).

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Reduced atrial natriuretic peptide concentrations in premenstrual syndrome

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Summary. Atrial natriuretic peptide (ANP) concentrations were determined by radioimmunoassay technique in 23 women, 11 women with premenstrual syndrome (PMS) and 12 comparable asymptomatic women. The asymptomatic women showed no change in ANP concentration during the menstrual cycle. In the PMS group ANP levels showed a significant fall in the midluteal phase compared to levels in the follicular phase. Throughout the cycle ANP concentrations were lower in the PMS group than in the comparison group. This difference was statistically significant in the early, mid and late luteal phases of the cycle. The lower ANP concentration in the PMS group in the luteal phases may indicate either a lower plasma volume or a decrease in the total body sodium content or both. These findings are contrary to those expected.

Although the premenstrual syndrome (PMS) was described by Frank (1931) more than 50 years ago, it still arouses a certain degree of scientific scepticism because of the inability to demonstrate specific biochemical or physical abnormalities in women with it. It is probable that an exaggerated response to the hormonal changes of the ovarian cycle is responsible for the diverse physical and psychological symptoms in PMS, as inhibition of the ovarian cycle appears to abolish these symptoms (Muse *et al.* 1984), and hormone replacement therapy causes PMS-like symptoms in some postmenopausal women (Hammarback *et al.* 1985). It seems likely that multiple factors are responsible for the symptoms. Suggested mechanisms include ovarian hormonal imbalance (Backstrom & Carstensen 1974; Dalton 1984), endorphin deficiency (Reid & Yen 1981), disordered essential fatty acid and prostaglandin metabolism (Jakubowicz *et al.* 1984), and water and sodium retention (Greenhill & Freed 1941). Many other mechanisms have also been postulated (O'Brien 1987). The phenomenon of premenstrual fluid retention is often mentioned, but the data available on this point are inconclusive.

Human α-atrial natriuretic peptide (ANP) is a 28 amino acid peptide with natriuretic, diuretic, renin-angiotensin and aldosterone antagonistic

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properties. ANP is secreted in response to increase in intravascular volume and sodium volume loading (Atlas & Laragh 1986).

It is possible that ANP may cause or reflect the fluid and electrolyte changes in PMS. We initiated the present study to investigate the possibility that the concentration of ANP may be altered in this condition.

Subjects and methods

Eleven women complaining predominantly of 'weight gain' and bloatedness were recruited from the Premenstrual Syndrome Clinic of the Royal Free Hospital. Twelve asymptomatic women selected from the hospital staff served as a comparison group (Table 1). Informed consent was obtained from all the women in the study. No woman suffered from cardiovascular or renal disease, or had a history of psychiatric illness. None of the women with PMS had used medication for at least 2 months before recruitment to the study and all were on an unrestricted diet. In the mid follicular and mid luteal days of the cycle each woman completed a general health questionnaire (GHQ), in order to exclude patients with an underlying psychological problem and the Moos' Modified Menstrual Distress Questionnaire (MDQ) to diagnose PMS, body weight was recorded after emptying the bladder. In addition prospective symptom assessment was made by completion of a daily linear visual analogue scale (VAS) for depression, irritability, headache, breast pain, bloatedness and subjective assessment of performance. Blood pressures were measured in both the follicular and the midluteal phases of the cycle. Serum progesterone measurements were made a week before the onset of the next predicted menstruation.

Table 1. Characteristics of women with premenstrual syndrome (PMS) and an asymptomatic comparison group

	PMS group ($n = 11$)		Comparison group ($n = 12$)	
Age (years)	28	(23–42)	25	(19–34)
Height (m)	1·60	(1·56–1·78)	1·61	(1·52–1·70)
Weight (kg)				
Follicular	70·7	(52·2–82·9)	61·1	(46·2–86·0)
Luteal	71	(52·8–83·8)	61·3	(46·0–86·0)
Blood pressure (mm Hg)				
Systolic				
Follicular	110	(90–120)	111	(90–140)
Luteal	108	(90–120)	107	(90–142)
Diastolic				
Follicular	70	(60–80)	73	(60–90)
Luteal	70	(60–80)	75	(62–85)

Results are median (range) values.

Blood samples were taken for ANP measurements in the follicular (Days 4–9), early (Days 16–18), mid (Days 19–22) and late (Days 23–26) luteal phases of the menstrual cycle. The samples, which were taken between 10.00 and 15.00 hours, with the women resting in the sitting position, were collected in tubes containing sodium EDTA (20 mg) and aprotinin (400 kallikrein units) and were immediately placed in ice. All samples were centrifuged within 1 h of collection at 2000 rpm for 10 min at 4 °C; plasma was separated and stored at −20 °C until assayed within 8 weeks of collection.

All samples were assayed together at the end of the study by radioimmunoassay techniques adapted from Sagnella & Macgregor (1984).

Extraction

Once the samples were thawed, the ANP was extracted from 5 ml plasma on Sep Pak C18 Cartridges (Water Associates, Milford MA) that had been previously activated by 5 ml methanol followed by 5 ml distilled water. The resin column was then washed with 5 ml distilled water and the adsorbed ANP was eluted with 4·5 ml of 80% ethanol in 4% acetic acid into glass tubes containing 100 μl of 1% bovine serum albumin. After evaporation to dryness at 50 °C under nitrogen, the dried residues were dissolved in 250 μl phosphate/triton buffer (50 mmol sodium phosphate, pH 7·4).

Plasma ANP extraction efficiency was determined by using plasma, supplemented with known amounts of 125-I labelled human ANP and extracted as described above. Analytical recovery was 95% (SD 5% $n = 20$).

ANP Assay

125-I labelled human ANP (Amersham International, Bucks, UK) was dissolved in 1 ml of assay buffer (phosphate/triton) and stored in aliquots, sufficient for a single assay, at −20 °C. ANP anti-serum raised in rabbits against synthetic ANP (Amersham International) was diluted in 12·5 ml of assay buffer and stored at

5 °C. The samples and standards were assayed in duplicate; each tube containing 50 µl aliquots of extracted plasma or standards, 50 µl of diluted anti-serum and 50 µl of labelled ANP. The mixture was then incubated for 24 h at 4 °C.

The unbound 125-I labelled ANP was then separated by precipitation with 250 µl dextran coated charcoal (0·8 g of Norit activated charcoal and 0·08 g dextran) in 50 ml assay buffer.

The supernatant containing the bound fraction was separated by centrifugation, and counted in a 'Selektronik' gamma counter. Standard curves were constructed using human α-ANP (Peninsular Laboratories, Merseyside, UK) dissolved in phosphate/Triton buffer to give a concentration of 1·0 to 600·0 pg per tube. Intraassay coefficient of variation was 9·6% ($n = 10$) and the interassay coefficient of variation was 12·5% ($n = 20$).

Statistical methods used were Wilcoxon rank sum test for paired data and Mann-Whitney *U*-test for unpaired data.

Results

The general health questionnaire scores (Table 2) were similar in the women with PMS and those in the comparison group during the follicular phase of the cycle but were increased in the luteal phase in the PMS group; the similarity in some questions in the GHQ and MDQ probably accounted for this. The women with PMS had significantly higher MDQ scores in the luteal than in the follicular phase of the cycle ($P<0·004$). The luteal phase scores in the PMS group were also significantly higher ($P<0·0001$) than those in the comparison group. Thus the diagnosis of PMS was confirmed and the possibility of the symptoms being due to psychiatric illness was reduced markedly.

In the PMS group the VAS scores for 'bloatedness' and the MDQ scores for 'water retention' differed significantly between the follicular and the luteal phases ($P<0·0004$, 0·008). No cyclical differences were seen for these scores in the control group (Fig. 1). Body weight (Fig. 1), and the systolic and diastolic blood pressures (Table 1) were similar in the two groups and did not change during the cycle. Progesterone concentrations were similar in both groups (Table 2).

The ANP concentrations showed no cyclical variation in the comparison group (Fig. 2). In the PMS group, ANP levels decreased significantly in the mid luteal phase of the menstrual cycle ($P<0·02$). The ANP concentrations in the PMS group were lower than in the comparison group throughout the menstrual cycle. This difference was statistically significant in the early, mid and late luteal phases of the cycle ($P<0·03$, 0·02, 0·04) (Fig. 2).

Discussion

This is the first report comparing ANP concentrations in women with well defined PMS and asymptomatic women. Tan *et al.* (1987) studied ANP in the menstrual cycle but did not refer to premenstrual symptomatology. The data obtained in a further study by Davidson *et al.* (1988) showed no variation in ANP during the cycle. This was not a controlled study comparing PMS women with asymptomatic controls and

Table 2. General Health Questionnaire (GHQ) and Moos' Menstrual Distress Questionnaire (MDQ) scores and serum progesterone in women with premenstrual syndrome (PMS) and an asymptomatic comparison group in the follicular and luteal phases of the menstrual cycle

Variable	PMS group ($n = 11$)	Comparison group ($n = 12$)	*P* value
GHQ			
Follicular	0 (0–15)	0 (0–13)	NS
Luteal	16 (4–27)	1·5 (0–18)	<0·0006
P	<0·05	NS	
MDQ			
Follicular	9 (0–24)	8·5 (0–50)	NS
Luteal	78 (54–98)	8·5 (0–41)	<0·0001
P	<0·004	NS	
Progesterone (nmol/l)			
Mid luteal	38 (2–94)	41 (5·1–60)	NS

Results are median (range) values

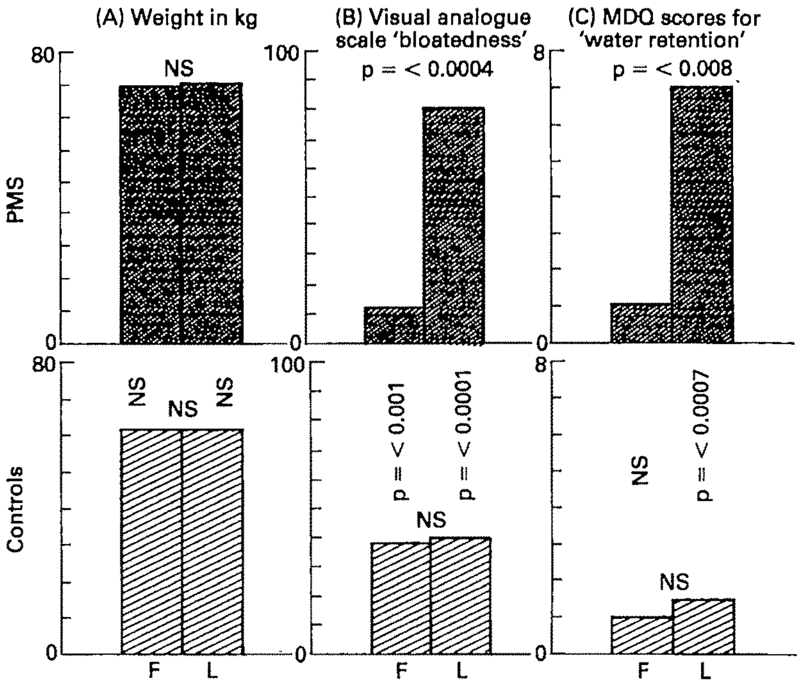

Fig. 1. Weight (kg), bloatedness (as in visual analogue scale) and water retention (as in Moos' Menstrual Distress Questionnaire) scores in women with premenstrual syndrome (PMS) and an asymptomatic control group in the follicular (F) and luteal (L) phases of the menstrual cycle.

the criteria used for the diagnosis of PMS were vague and methods of symptom quantification were not discussed. There was no mention of weight gain and bloatedness was assessed subjectively.

Our data show that plasma ANP concentrations altered during the menstrual cycle, the PMS group showing a significant fall from the follicular to the mid-luteal phase, in contrast to the findings of Davidson *et al.* (1988). These authors may have missed this decrease in the mid luteal phase because of infrequent sampling and insufficient numbers of subjects.

There were no changes in body weight or blood pressure in either group in our study and therefore we cannot explain the lower ANP concentrations observed in the PMS group. Dietary intake was also similar in both groups and thus could not account for these differences.

If salt and water retention were responsible for the symptoms of PMS, in particular bloatedness, then ANP concentrations should have been higher in the symptomatic group. The lower plasma ANP concentrations in the PMS group when compared with the asymptomatic group were thus contrary to our expectations. Andersch *et al.* (1978) demonstrated the absence of significant change in total body water, although they observed a significantly higher water/potassium ratio in the luteal phase in those with PMS. They suggested that there was a redistribution of fluid rather than an increase in the total body water.

Our results may reflect a lower intravascular volume secondary to redistribution of fluid into the extracellular compartment in women with PMS.

The sodium retaining effect of aldosterone is opposed by ANP. Aldosterone levels are higher in the luteal phase of the menstrual cycle, perhaps secondary to the natriuretic effect of progesterone. Janowsky *et al.* (1973) found increased urinary potassium/sodium ratios in the late luteal phase, thus hypothesizing increased

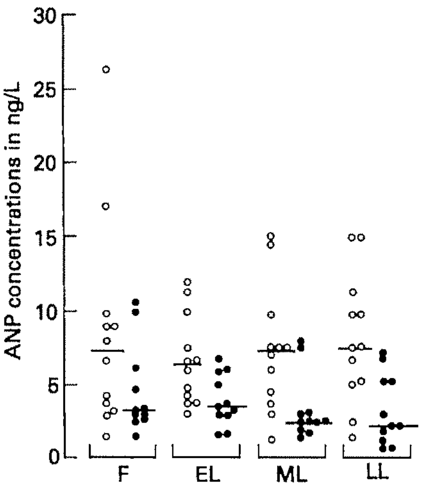

Fig. 2. Atrial natriuretic peptide concentrations in women with premenstrual syndrome (●: PMS group) and asymptomatic women (O: comparison group) during the menstrual cycle (F = follicular; EL = early luteal; ML = mid luteal; LL = late luteal). Statistically significant differences (P = <0·04–<0·02) were seen throughout the luteal phases between the PMS and comparison groups and between the follicular and mid luteal phases in the PMS group.

aldosterone secretion. However, they did not specifically select women with PMS. Later studies by Munday *et al.* (1981) and O'Brien *et al.* (1979) reported that aldosterone concentrations were increased in both asymptomatic women and in women with PMS in the luteal phase of the cycle, but O'Brien *et al.* (1979) demonstrated a lower rise in aldosterone concentrations in the women with PMS.

It may be that in women with PMS, insufficient aldosterone is secreted premenstrually to counter-balance the effects of progesterone. Thus unopposed progesterone-induced-natriuresis occurs altering the urinary Na:K ratio. Our present results support this theory as ANP levels were found to be lower in women with PMS and this could be secondary to lowered total body sodium.

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The availability of epidural anaesthesia and analgesia in obstetrics

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Summary. This survey analyses the provision of obstetric epidural services on national and regional bases and also by size of obstetric unit. Epidural anaesthesia and analgesia in obstetrics is not readily available to all women who wish for it, or in whom it is recommended on medical grounds, in spite of the recommendations of the Social Services Committee and other advisory bodies. Deficiencies in the provision of facilities are obvious but further analysis at a local level is required to determine the reasons and the remedies.

Of the several options for pain relief in labour and for operative delivery, epidural analgesia has been used increasingly in the United Kingdom because of consumer demand, effectiveness and relative safety for the woman and her baby, especially when compared with general anaesthesia for operative delivery. The availability and use of epidural anaesthesia is sometimes quoted as an index of the quality of an obstetric anaesthetic service. The Social Services Committee (1980) recommended that there should be an epidural service in all consultant units and a Report of the National Medical Consultative Committee for Scotland (1985) stated that 'An optimum obstetric anaesthesia and analgesia service is one which provides all forms of anaesthesia and analgesia for all women who wish or require such a service at all times . . . Without the availability of epidural analgesia for labour and for all types of operative delivery, including caesarean section, modern obstetric practice is incomplete.'

Epidural analgesia makes considerable demands on the time of obstetric anaesthetists and is therefore relatively expensive unless optimal use is made of their time, i.e., there is a sufficient workload; this is a product of demand and size of unit.

The present review was undertaken to study the use of epidural anaesthesia in the United Kingdom.

Source of data and methods

All obstetric units recognized by the Royal College of Obstetricians and Gynaecologists for training purposes are required to submit an annual statistical return to the Hospital Recognition Committee. Information was obtained from these annual returns, covering 271 units for the years 1982–86 inclusive. This represents approximately 3·4 million deliveries and 565 000 epidural blocks and is similar to the proportion reported for a survey covering 203 units over the same 5-year period (Scott & Hibbard 1990). Epidural data returns used in the present study did not distinguish between relief of pain in labour and use for operative delivery, but the associated study, based on a questionnaire, showed that apparently 16% of epidural blocks were given for caesarean section. Where an annual return was missing, or incomplete, interpolated means were calculated.

Although data were obtained for individual hospitals, valid comparisons are difficult

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because of factors such as the nature of the local population served and selection of cases, especially in regional referral centres. Also it is not always possible to make a clear distinction between 'teaching' and 'non-teaching' hospitals. Therefore the analysis is primarily concerned with regional variations as this gives a better indication of facilities that are geographically reasonably available to a population, assuming some choice of unit for delivery.

Results

The overall epidural rate for the 5-year period in the United Kingdom was 17%, with national rates ranging from 21% for Scotland to 6% for Northern Ireland (Fig. 1). In England there were significant regional variations, from 26% in the Trent region to 10% in the NE Thames region.

Figure 2 shows the distribution of epidural rates by units. Overall, 31% of the units had rates of ≤5% (19% had rates <2%) whereas 21% had rates >25% and 10 units had rates >40%, with a maximum of 51% in one unit.

Epidural rates were also considered in relation to unit size, classifying those with over 3000 deliveries as 'large', 1500–3000 as 'intermediate' and less than 1500 deliveries as 'small'. In general, epidural rates tended to be higher in large units (Table 1), but there were considerable variations, with a rate as low as 0·2% in one large unit and as high as 35% in one small unit.

The regional variations referred to above were further analysed by unit and unit size. In Table 2 the data for the two regions with the highest rates, and the region with the lowest rate and Wales, are summarized. Again a wide range is seen for each region and also for 'large' units in those regions. Further, the mean regional rate does not appear to be directly influenced by the size of units. For example, the epidural rate for NW Thames is about twice that for NE Thames, yet NW Thames has more 'small' units and fewer 'large' units.

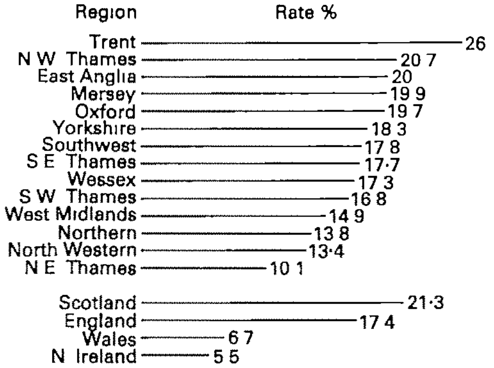

Fig. 1. Mean epidural rates—United Kingdom by regions 1982–1986

Discussion

The wide variation in the use of epidural anaesthesia between regions, with a nearly five-fold difference between the rates in the highest and lowest regions, must give rise to concern in a health service which has, as an objective, equality of availability of health services for all. Certainly the recommendations of the Social Services Committee have not been fully implemented and in recent regional surveys it was found that in Wales only 5 of 20 units could offer an 'on request' epidural service (Welsh Office, 1986), whilst in the Yorkshire region 9 of 19 units provided such a service (MacDonald & Webster, 1980). A survey in the SE Thames region (1985) showed that epidural analgesia was not available in 10 of the 25 units.

There is no consensus view for an optimal obstetric epidural rate, but the mean rate for the UK in this study was 17%, the same as that in the National Birthday Trust Survey (Morgan 1987). Although this figure is influenced by the number of units where a full epidural service is not freely available, it is also close to the figure which has been obtained in some other studies, such as that in Cardiff (Hibbard *et al.* 1979), where free availability of an epidural service on demand results in a similar uptake. Whatever the optimal figure may be, unduly low rates might reflect

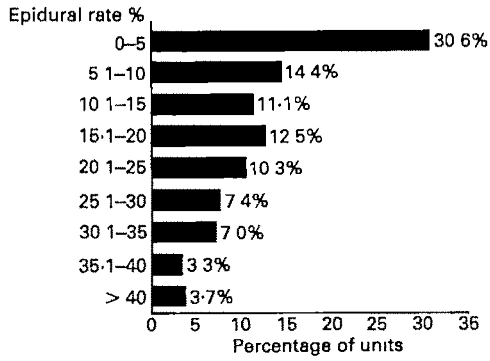

Fig. 2. Epidural analgesia rates—distribution in 271 units.

Table 1. Epidural rates and size of unit

Size of unit (No. of deliveries)	No. of units	Range of epidural rate (%)	No. of units by epidural rates (%)					
			0–10		10·1–20		>20	
			n	(%)	*n*	(%)	*n*	(%)
>3000	73	0·2–51	18	(28)	22	(30)	33	(45)
1500–3000	145	0–45	65	(45)	35	(24)	45	(31)
<1500	53	0–34	38	(72)	7	(13)	8	(15)

under-provision and it is notable that 31% of units had a rate of ≤5%. Unduly high rates might indicate biased advice favouring epidural analgesia. In either case there are suggestions of inappropriate resource allocation.

Are rates in the lower ranges found in this study acceptable or desirable? The lack of uptake may be due to lack of demand which may be due to lack of available information or to racial, cultural, religious and other social factors. On the professional side there may not be enough fully trained staff to manage the service. A further factor is that there may be lack of motivation in providing a service, possibly related to lack of facilities and failure to press for adequate resources.

On the other hand are high rates necessary or desirable? Clearly in some regions the demand exists, but it is not clear to what extent this is generated primarily by the women themselves or to what extent it is fostered directly or indirectly by the professionals.

There is no evidence that a high epidural rate for pain relief, as opposed to anaesthesia for operative delivery, is necessary and the resource implications of a high rate are considerable. But it is accepted that of the commonly available methods, epidural analgesia gives the best pain relief in labour, a view supported in at least one consumer survey (Morgan *et al.* 1984). It also has significant advantages for the baby, especially in a number of high risk situations, such as preterm delivery and in pre-eclampsia and also when used as an alternative to general anaesthesia for operative delivery. It is therefore necessary to look for methods of increasing availability in the apparently deprived areas.

There is a case for increase in resource allocation in all units which have inadequate facilities, but to offer a full service would be uneconomic in smaller units and it is unlikely that adequate skilled staff could be provided, even if funding was available. The transfer of resources between obstetric units to achieve a better balance might seem administratively attractive but could lead to a generally inferior service. There is no evi-

Table 2. Comparison of regions in England and Wales with highest and lowest epidural rates

Size of unit (No. of deliveries)	No. of units			
	Trent	NW Thames	NE Thames	Wales
>3000	7	3	6	2
1500–3000	8	12	11	9
<1500	2	5	0	5
Total	17	20	17	16
Epidural rate (%)				
Mean	26	21	10	7
Range	1–45	0·4–5	0·3–35	0·4–20
Range for units with >3000 deliveries	11–44	9–51	0·8–19	1·4, 3·5

dence of over-staffing with obstetric anaesthetists in any unit and few come up to the recommended levels of the Association of Anaesthetists (1987).

As an alternative strategy, women from areas lacking an appropriate service, who express a specific desire for epidural analgesia, could be transferred to major centres which would be upgraded, if necessary, to provide sufficient facilities. This concept is recommended in 'Anaesthetic Services for Obstetrics' (1987) which states that: 'Mothers should be given information if the range of anaesthetic services available in a unit is restricted. Admission to a unit with a comprehensive service should be offered as an alternative'. The inconvenience of distance might be an acceptable price for a woman to pay to have a service which she desires. However, this would not provide for patients in whom specific obstetric indications for epidural analgesia may arise, or those who change their minds after the onset of labour, and in whom safe transfer is not feasible. Could facilities be provided locally for this limited number of women in their own district? If not, they would be deprived of a medically beneficial facility and this raises the question of whether units that cannot provide full facilities should continue to exist.

The patchy nature of epidural availability also raises questions concerning professional training. Efforts are made to ensure that trainee anaesthetists acquire adequate experience in the technique but there is no evidence that a trainee obstetrician will, at least at some stage in his career, work in a unit where a full epidural service (or indeed even an attenuated service) is established.

Whilst such organizational and logistic debates continue, it is equally important that we continue to look for other equally effective and safe methods of pain relief which are less demanding on resources, and to modify epidural techniques to reduce the need for professional supervision presently inherent in the achievement of safety.

Epidural anaesthesia and analgesia in obstetrics is not readily available to all women who wish for it, or in whom it is recommended on medical grounds, in spite of the recommendations of the Social Services Committee and other advisory bodies. The support given by both Government and professional bodies for a freely available epidural service has clearly not been universally supported at regional or district level and these problems need to be addressed by regional health authorities and their advisers.

Acknowledgment

This paper was prepared on behalf of the Joint Standing Committee on Obstetric Anaesthesia and Analgesia of the Royal College of Obstetrics and Gynaecologists and the College of Anaesthetists. B. M. Hibbard, RCOG (Chairman), B. V. Lewis, RCOG, C. H. Rodeck, RCOG, M. Rosen, CA, A. P. Ruben, CA, D. B. Scott, CA.

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The placental transfer of mifepristone (RU 486) during the second trimester and its influence upon maternal and fetal steroid concentrations

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Summary. A double-blind, placebo-controlled study has assessed the maternal and fetal endocrine effects of the maternal administration of the anti-progestin mifepristone in mid-pregnancy. There were six women in each group. Four hours after oral administration of 600 mg mifepristone, the drug was detected in both maternal and fetal circulations and in the amniotic fluid. No significant changes in progesterone, cortisol, oestradiol, or aldosterone concentrations were detected in the maternal circulation after treatment with mifepristone or placebo. In women treated with mifepristone, the mean fetal aldosterone level was 1699 (SD 217) pmol/l which was significantly higher than the mean level of 999 (SD 84) pmol/l in the control group but no significant changes occurred in the fetal progesterone, oestradiol or cortisol concentrations. The significance of these results is discussed in relation to the possible therapeutic uses of mifepristone for inducing labour.

Mifepristone (17β-hydroxyl-11 β-4 dimethylamino-phenyl-17α-1 propynyl esta-4, 9 dien-3-one (RU 38,486); Roussel-Uclaf, Romainville. France), a synthetic derivative of norethidrone, is a competitive progesterone receptor antagonist.

In a small study, oral administration of mifepristone before intrauterine prostaglandin treatment during the second trimester has been shown to significantly reduce the induction–abortion interval and thus lower the dose of prostaglandin required and consequently reduce the frequency of associated side-effects (Urquhart & Templeton 1987).

It is possible therefore that if this potentiating effect on prostaglandin treatment could operate also in the third trimester, mifepristone might be used to improve the outcome of induced labour. The drug is known to have both anti-progesterone (Baulieu 1985) and anti-glucocorticoid (Bertagna *et al.* 1984) effects, both of which may have clinically significant effects on the fetus. The aim of this study was to assess the placental transfer of mifepristone and to investigate its possible effects on fetal plasma steroid concentrations.

Subjects and methods

A double-blind placebo-controlled study was designed to include 12 women at 16–19 weeks gestation who were scheduled for termination by intra-amniotic injection of prostaglandin within the terms of the 1967 Abortion Act. All the women gave informed consent, and local ethics committee support was obtained for the study. Menstrual dates were confirmed by ultrasono-

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graphy and the women were allocated to receive either mifepristone or identical placebo tablets using a predefined randomization code, which was held by Roussel UK Ltd, Uxbridge.

The women received 600 mg of mifepristone or placebo orally at 09·00 hours on the day of admission. Before treatment and then hourly for 4 h, the women were questioned about uterine pain, vaginal bleeding and symptoms which could have been due to the drug. A peripheral venous blood sample was collected immediately before treatment (pretreatment sample) and analyzed for haematological (haemoglobin, group) and hormonal (β-hCG, progesterone, oestradiol, cortisol and aldosterone) concentrations. Four hours after treatment and immediately before fetal blood sampling, a further maternal blood sample (post-treatment sample) was collected to measure levels of mifepristone and its major metabolite, RU 42,633, progesterone, oestradiol, cortisol and aldosterone.

The women were given 10 mg of diazepam intravenously and a 5 ml sample of amniotic fluid was taken for analysis from each woman before fetal blood sampling using the technique described by Westgren *et al.* (1988), as modified by Selinger *et al.* (1987). Heparinized syringes were used to aspirate 3 ml of fetal blood which was later analyzed for mifepristone and its metabolite RU 42,633, progesterone, oestradiol, cortisol and aldosterone concentrations. After collection of the amniotic fluid and fetal blood samples, PGE_2, 5 mg, was injected into the amniotic cavity. Six hours later an intravenous infusion of oxytocin, 100 m-units/ml, was started and maintained until abortion. Subsequent management was as described previously by Hill & MacKenzie (1989). The induction-to-abortion interval was defined as the time from prostaglandin treatment to expulsion of products of conception.

All plasma samples were stored at −20°C until the clinical studies had been completed and each steroid assay was done as a single run. Progesterone, oestradiol, cortisol and aldosterone levels were assayed using commercial radioimmunoassay kits supplied by Diagnostic Products UK Ltd, Abingdon, Oxford. The specificity of the steroid assays was progesterone 2·4%, oestradiol 1·8%, cortisol 1·5% and aldosterone 0·6%. Mifepristone and RU 42,633 assays were performed by Roussel-Uclaf, Romainville, France, using a radioimmunoassay technique described previously by Salmon & Mouren (1985).

Results

Table 1 shows that the two groups were similar in age, height, weight, gestational age, β-hCG, and parity. No drug reactions or side-effects were recorded after mifepristone treatment and no patient had vaginal bleeding or uterine pain before prostaglandin treatment.

The mean induction–abortion interval was 17·2 (SD 8·6) h in the mifepristone group and was not significantly different from the interval of 16·1 (SD 7·7) h in the placebo group. All the women aborted without complications and left hospital within 48 h of admission.

Concentrations of mifepristone and RU 42,633

The maternal:fetal ratios for mifepristone and RU 42,633 were 9:1 and 17:1 respectively; individual values of mifepristone and RU 42,633 concentrations in maternal and fetal plasma and in amniotic fluid are illustrated in Fig. 1. The mean maternal plasma mifepristone concentration was 2·7 (SD 2·2) μmol/l which was significantly higher than the fetal plasma concentration of 0·3 (SD 0·1) μmol/l and amniotic fluid concentration 0·2 (SD 0·1) μmol/l ($P<0·05$, Mann–Whitney *U*-test). There was a similar relation for RU 42,633 concentration between the mean maternal plasma 3·6 (SD 1·6) μmol/l, fetal plasma 0·2 (SD 0·1) μmol/l and amniotic fluid 0·1 (SD 0·06) μmol/l ($P<0·05$, Mann–Whitney *U*-test).

Maternal steroid levels

Table 2 illustrates the mean (SD) concentrations of steroid in the maternal plasma at the two sampling times for the two groups. There were no significant differences between the pre- and post-treatment concentrations between treated

Table 1. Characteristics of women treated with mifepristone or a placebo

Variable	Mifepristone (n = 6)	Placebo (n = 6)
Age (years)	22·3 (3·0)	23·8 (2·8)
Height (cm)	163 (4·9)	161 (5·1)
Weight (kg)	62·8 (4·5)	60·9 (6·7)
Gestation (weeks)	17·0 (0·6)	16·5 (0·8)
β-hCG (iu/l)	11 848 (5561)	11 762 (8318)
Nulliparae *n* (%)	4 (66·6)	3 (50)

Results are mean (SD) values

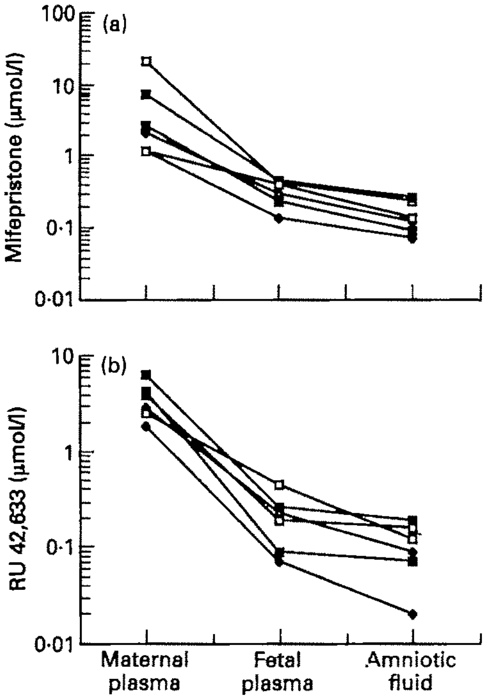

Fig. 1. Individual mifepristone (a) and its metabolite, RU 42,633 (b) concentrations in maternal and fetal plasma and amniotic fluid samples 4 h after maternal ingestion of mifepristone ($n = 6$).

and control patients (Wilcoxon's two-sample test). There were also no significant differences in progesterone, oestradiol, cortisol, or aldosterone between the patients who received mifepristone and the placebo group (Mann–Whitney *U*-test).

Fetal steroid levels

Table 3 gives the mean fetal plasma steroid levels and Fig. 2 shows the relation between fetal and maternal progesterone, oestradiol, cortisol, and aldosterone levels. Progesterone levels were always higher in fetal than in maternal circulations in both groups, whereas cortisol concentrations were always higher in maternal than in fetal samples. There was no consistent relation between the maternal and fetal oestradiol and aldosterone levels. There were no significant differences in the fetal plasma concentrations of progesterone, oestradiol or cortisol between the two treatment groups. In the mifepristone group the mean fetal aldosterone concentration was 1699 (SD 217) pmol/l which was significantly higher than the mean concentration of 999 (SD 84) pmol/l in the placebo group ($P<0·05$, Mann–Whitney *U*-test). There was no correlation between mifepristone or RU 42,633 and fetal steroid levels.

Discussion

Mifepristone has been shown to have a ripening effect on the cervix during the first trimester (Durlot *et al.* 1988; Frydman *et al.* 1988; Radestad *et al.* 1988; Ulmann & Dubois 1988), and to result in spontaneous expulsion of the dead fetus in the second and third trimester of pregnancy (Cabrol *et al.* 1985; Padayachi *et al.* 1988). It is therefore possible that the drug could be used to ripen the unfavourable cervix and induce labour. Observations in primates are encouraging (Wolf *et al.* 1989). Before proceeding to explore the use of mifepristone for these purposes in women it is necessary to have a greater understanding of the placental kinetics of the drug and its effects on the fetus. To our knowledge, this is the first study describing the effects

Table 2. Maternal peripheral venous steroid levels 4 h after treatment with mifepristone or placebo

		Sampling time	
Steroid	Group	Pretreatment	Post-treatment
Progesterone	Mifepristone	147 (48)	126 (67)
(nmol/ml)	Placebo	140 (44)	131 (56)
Oestradiol	Mifepristone	17·4 (2·9)	16·4 (7·3)
(nmol/l)	Placebo	14·2 (7·4)	10·5 (6·5)
Cortisol	Mifepristone	703 (161)	669 (183)
(nmol/l)	Placebo	620 (363)	624 (239)
Aldosterone	Mifepristone	878 (524)	810 (879)
(pmol/ml)	Placebo	822 (384)	901 (457)

Results are mean (SD) values. There were six women in each group.

Table 3. Fetal steroid levels 4 h after maternal treatment with mifepristone or placebo

Steroid	Treatment group Mifepristone ($n = 6$)	Placebo ($n = 6$)
Progesterone (nmol/l)	1693 (487)	1288 (380)
Oestradiol (nmol/l)	13·9 (3·5)	10·2 (2·2)
Cortisol (nmol/l)	53·2 (13·2)	42·2 (17·2)
Aldosterone (pmol/l)	1699* (531)	999* (206)

(*$P<0·05$, Mann-Whitney *U*-test).
Results are mean (SD) values.

of mifepristone on fetal plasma steroid concentrations in human mid-pregnancy.

Frydman *et al.* (1985) demonstrated transplacental passage of mifepristone in second-trimester termination of pregnancy, and found an exponential increase in drug concentration in the fetus with time. The lowest level (20 ng/ml) was found 30 min and the highest (400 ng/ml) 18 h after oral administration. Wolf *et al.* (1988) reported transplacental passage of mifepristone within 2 h of oral ingestion during the second or third trimester of pregnancy in cynomolgus monkeys; they concluded that there was only minimal resistance to 'free' passage of mifepris

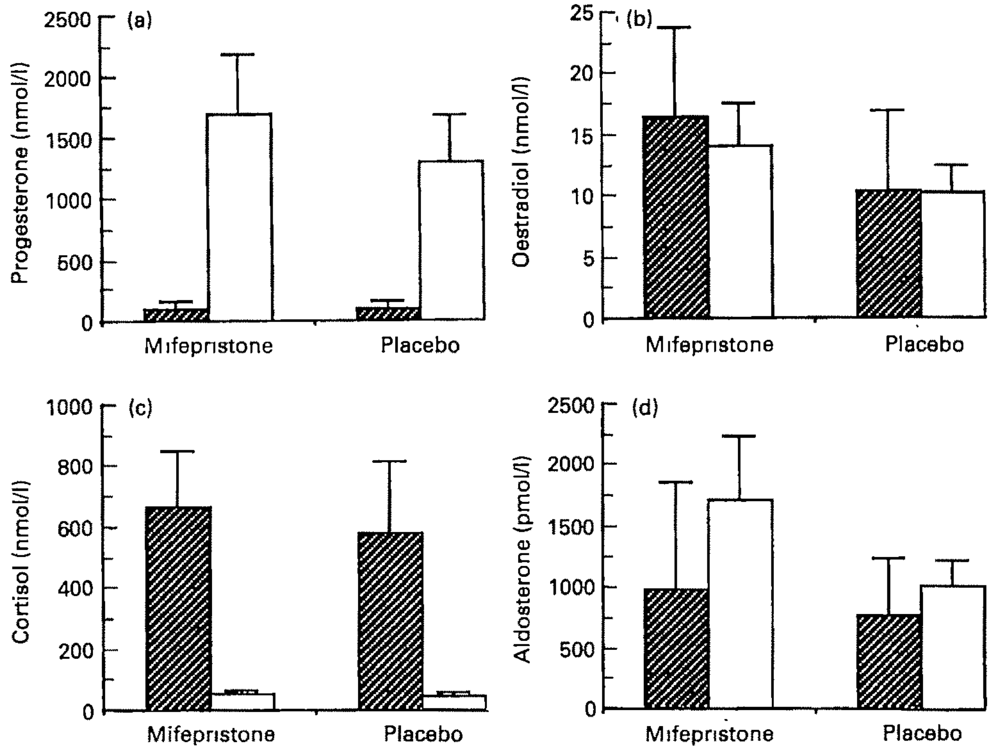

Fig. 2. Progesterone (a), oestradiol (b), cortisol (c), and aldosterone (d) concentrations in paired materna (▨) and fetal (□) blood samples in six women after treatment with mifepristone and six treated wit placebo.

tone across the placenta. The maternal: fetal ratio fell from 3:1 in the second trimester to 6:1 in the third trimester, indicating that the efficiency of placental transfer may decrease as pregnancy advances The authors postulated that the bioavailability of mifepistrone may decrease significantly with gestation and the theoretical risks of fetal side-effects could be reduced in late pregnancy.

Our results indicate that both mifepristone and probably its metabolite, RU 42,633, rapidly cross the placenta and can be found in both fetal plasma and amniotic fluid within 4 h of maternal ingestion. Compared with other drugs such as PGE_2 (MacKenzie *et al.* 1989) and mefenamic acid (MacKenzie *et al.* 1985), where the maternal:fetal radio is approximately 3:1, the concentration of mifepristone in the fetal circulation is low (9:1). This relatively low fetal concentration could be due to rapid transfer and metabolism or impeded transfer across the placenta, or protein or receptor binding.

At the time of fetal blood sampling there were no changes in the fetal concentrations of progesterone or oestradiol in the mifepristone group compared with control subjects. Selinger *et al.* (1988) demonstrated a 89% and 91% reduction in maternal progesterone and oestradiol concentrations 3 h after treatment with the antiprogestin, epostane, a 3-β hydroxysteroid dehydrogenase inhibitor, in the second trimester. They also demonstrated a statistically significant decrease in fetal progesterone, but not oestradiol, concentrations after epostane treatment, but could not detect any epostane in the fetal circulation or amniotic fluid at this time. Our failure to demonstrate any significant maternal or fetal changes after treatment with mifepristone probably reflects the difference in mode of action between the two drugs.

Mifepristone is known to block the glucocorticoid negative feedback effect at the pituitary gland and therefore induces a compensatory increase in plasma ACTH and cortisol (Nieman & Loriaux 1988). In this study, although ACTH was not measured, no change in maternal or fetal cortisol concentrations was demonstrated, and the fetal levels were in the expected range (Lopez Bernal & MacKenzie 1987). The failure to demonstrate any significant change in fetal cortisol levels may be of clinical importance because any withdrawal of cortisol at a cellular level, due to blockage of the glucocorticoid receptors, could have a detrimental effect upon fetal lung maturation due to decreased surfactant production (Bertagna *et al.* 1988).

An unexpected finding was the significantly higher fetal aldosterone concentrations after maternal ingestion of mifepristone. M. L. Swahn *et al.* (unpublished data) found an elevation in aldosterone in maternal plasma on the second of a 4-day treatment with mifepristone (25 mg twice daily), but this increase was not sustained in spite of persistent elevation in cortisol. No other studies on mifepristone have reported an increase in maternal aldosterone concentrations. Fetal aldosterone levels have been measured in the umbilical cord at the time of delivery, and have been found to be higher (Beitins *et al.* 1972) and lower (Sippell *et al.* 1979; Dorr *et al.* 1987) than the maternal levels, depending on the study. However, little is known about fetal aldosterone levels in the second trimester, and no significant changes in fetal aldosterone concentrations were demonstrated after treatment with epostane at this gestation (Selinger *et al.* 1988). The importance of the increased fetal aldosterone concentrations after maternal treatment with mifepristone is uncertain, the increase may be due to mifepristone blocking fetal mineralocorticoid receptors, but if this had occurred a corresponding increase in maternal concentrations might have been expected; also mifepristone is thought not to block these receptors. The number of women in each group was small and the increase in fetal aldosterone levels only just reached statistical significance, so this may have occurred by chance. Similarly, in view of the small number of women studied, any effect of mifepristone on the other steroids studied cannot be totally excluded, therefore further studies are planned to investigate the effect of the anti-progestin on fetal steroid levels.

The use of mifepristone provides an exciting new concept that has the potential for improving the outcome of induced labour, but more studies on the fetal endocrine effects are necessary before it can be explored in continuing pregnancies in humans. Studies are required to investigate the effects of maternal treatment with mifepristone on the fetus 24–48 h after treatment since it appears that a separating period of this duration may be necessary before clinical benefits can be seen (Swahn & Bygdeman 1988). In addition, careful long-term studies will be required to assess any possible delayed consequences for the newborn.

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Preventing IUCD-related pelvic infection: the efficacy of prophylactic doxycycline at insertion

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Summary. Most of the small increased risk in pelvic inflammatory disease (PID) associated with the intrauterine contraceptive device (IUCD) appears to be caused by bacterial contamination of the endometrial cavity at the time of insertion. This randomized clinical trial of 1813 women in Nairobi, Kenya, assessed the effectiveness of 200 mg of doxycycline given orally at the time of insertion in reducing the occurrence of PID. The rate of this infection in the doxycycline-treated group was 31% lower than that in the placebo-treated group (1·3 and 1·9%, respectively; RR 0·69; 95% CI 0·32 to 1·5). The rate of an unplanned IUCD-related visit to the clinic was also 31% lower in the doxycycline-treated group (RR 0·69; 95% CI 0·52 to 0·91). Although the significance level ($P = 0{\cdot}17$) for the reduction is PID does not meet the conventional standard of 0·05, the results may be suggestive of an effect. Moreover, the reduction in IUCD-related visits ($P = 0{\cdot}004$) not only represents an important decrease in morbidity but also substantiates the reduction found for PID. Further studies are needed to corroborate these results. Consideration should be given to the prophylactic use of doxycycline at the time of IUCD insertion as an approach to preventing PID and other IUCD-related morbidity.

Most pelvic inflammatory disease (PID) associated with use of an intrauterine contraceptive device (IUCD) appears attributable to bacterial contamination of the endometrial cavity at the time of insertion. That contamination routinely occurs has been observed for over two decades

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(Mishell *et al.* 1966). Results from a number of studies (Vessey *et al.* 1981; Booth *et al.* 1980; O'Brien *et al.* 1983; Lee *et al.* 1983) have shown that the risk of PID was inversely related to the duration of IUCD use. In the largest and most detailed of these (Lee *et al.* 1983), the risk of PID (excluding women using the Dalkon Shield) was significantly elevated only during the first 4 months of use. The relative risk (RR) compared with women not using contraception was highest in the first month (RR = 3·8). The additional risk was lower at 2–4 months (RR = 1·7) and almost absent at ≥5 months (RR = 1·1). Thus, both bacteriological and epidemiological studies implicate endometrial contamination at IUCD insertion in the development of PID. Since use of prophylactic antibiotics in women having an induced abortion appears to reduce the risk of subsequent infectious morbidity by about 50% (Grimes *et al.* 1984; Park *et al.* 1985), we conducted this randomized clinical trial to investigate whether use of prophylactic antibiotics at IUCD insertion would have an analogous protective effect.

Subjects and methods

From December 1984 to January 1986, all women requesting an IUCD at the Family Welfare Centre, Kenyatta National Hospital, who were menstruating regularly and who were between 20 and 44 years of age, were candidates for inclusion in the study. They were not admitted to the study if any of the following criteria were present: (1) a history of ectopic pregnancy, (2) pregnancy within the past 42 days, (3) leiomyomata of the uterus, (4) active PID, (5) a cervical or endometrial malignancy, (6) a known hypersensitivity to tetracyclines, (7) use of any antibiotics within the past 14 days or long-acting injectable penicillin, (8) an impaired response to infection, or (9) residence outside the city of Nairobi, insufficient address for follow-up, or unwillingness to return for follow-up. As a result, 470 women were excluded from the study, most due to exclusion criterion 9. Informed written consent was obtained before entry into the study; 75 women refused to participate, 57 because of time constraints on the day of insertion.

Trial design

The study was a double-blind, randomized clinical trial of the efficacy of a single oral dose of prophylactic doxycycline (Pfizer Limited, Sandwich, UK) versus placebo given at the time of IUCD insertion in preventing PID. The study was approved by the institutional review board. Women were randomized only after admission criteria were met on the day of the planned IUCD insertion, and eligibility had been assured by the physician. Women had an equal probability of assignment to the groups. The randomization code was developed using a computer random number generator to select random permuted blocks. The block lengths were 4, 8 and 10, varied randomly every 200 women (Friedman *et al.* 1984). No exclusions of women after randomization were allowed.

The doxycycline and placebo were in capsule form and identical in appearance. They were prepacked in bottles and consecutively numbered for each woman according to the randomization schedule. Each woman was assigned an order number and received the capsules in the corresponding prepacked bottle. This scheme effectively blinded the randomization process. Doxycycline was chosen for prophylaxis because of its broad spectrum, long half-life, excellent gastrointestinal absorption, selective concentration in the endometrium, and low cost (Grimes *et al.* 1984).

The randomization code was kept in the USA. Thus, all administration and assessments were done blinded to treatment assignment, and the investigators and patients were also blinded to the ongoing results of the study. The code was broken only after data collection had been completed.

Regimen

The doxycycline and placebo were both supplied as two capsules. The physician who administered the treatments at the time of randomization observed carefully that the capsules were ingested to assure compliance. The therapies were administered at least 1 h before IUCD insertion to allow for systemic absorption of the drug. The implementation of this trial within the clinic did not alter the choice of IUCD type. When the study began, the Lippes loop was used by most women, with the Copper T, Nova T, and Multiload being used less frequently. (Brand names are used for identification only and do not imply endorsement by the USPHS or any of its agencies.) IUCDs were inserted by clinic nurses as is the standard practice.

Withdrawals and deviations

The women who entered the trial remained in the allocated study group for analysis regardless of subsequent management. Antibiotics or other treatments for PID were not given at our study facility unless PID was diagnosed. However, women enrolled in the study were treated appropriately for other illnesses which occurred during the follow-up period.

Endocervical cultures

Endocervical specimens for culture of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* were taken before insertion of the IUCD. For culture of *N. gonorrhoeae,* a cotton-tipped swab was used to inoculate Thayer-Martin medium. Plates were incubated at 35°C in candle jars and examined at 48 and 72 h. Colonies typical of *N. gonorrhoeae* were confirmed by Gram stain appearance and oxidase positivity. For culture of chlamydia, a second, dacron-tipped, metal or plastic swab was rotated in the endocervical canal for 5–10 s. The swab was placed into 2-SP transport media and held at 4°C until transported to the laboratory where it was kept at −80°C until inoculated on to cycloheximide-treated McCoy cells and centrifuged at 2800 *g* for 1 h. Cells were incubated for 72 h and stained with fluoresceinated monoclonal antibody (Syva Company, Palo Alto, CA, USA).

Measurement of outcome

The women were asked to return to the clinic 1 month after IUCD insertion. This extended occasionally to 6 weeks to allow for follow-up of women who had not returned when scheduled. Complete information, including an assessment for PID, was recorded at this 1-month visit for all women returning. Throughout the first month, all women were assessed for PID whenever they returned for an unscheduled IUCD-related visit.

PID was assessed clinically by the gynaecologists responsible for admitting and assessing all the women in the study. The primary outcome variable of interest was the frequency of PID during the first month after insertion. The important secondary outcome variable was the frequency of an unscheduled visit for an IUCD-related problem during the first month. The criteria used for diagnosis of PID were those suggested by the Infectious Disease Society for Obstetrics and Gynecology in the United States (Hager *et al.* 1983). A diagnosis of PID was made only if the following three tenderness criteria were identified: abdominal direct tenderness, tenderness with motion of cervix and uterus, and adnexal tenderness, together with at least one of the following five objective criteria (1) Gram-negative intracellular diplococci identified in endocervical swabs, (2) pyrexia >38°C, (3) leucocytosis >10 000 WBC/µl, (4) purulent material from peritoneal cavity obtained by culdocentesis, or (5) pelvic abscess or inflammatory complex on bimanual examination.

Sample size and statistical analysis

We calculated a requisite study sample size of at least 1800 women (900 in each group) by assuming an estimated incidence rate of PID in the placebo group of 4% and our desire to detect a true 50% decrease in the prophylactic doxycycline group. We used a one-sided alpha-error of 0·05, and a power of 0·80. We decided upon one-sided tests because we were only interested in whether doxycycline was more effective than placebo (Pocock 1983). Having calculated our sample size based on the probable occurrence of PID, we knew our analyses of unplanned IUCD-related visits would have more than sufficient power.

Mantel-Haenszel chi-tests were used for the one-tailed comparisons of prophylactic doxycycline patients with placebo patients on dichotomous outcome variables (Rothman & Boice 1979; Rothman 1986). χ^2-tests were used for the two-tailed comparisons of patient characteristics. One-way analyses of variance were used for comparisons on interval-scaled variables. In analysing dichotomous outcome variables, the effects of potential confounding variables, even though very unlikely because of the randomized design, were controlled for by the Mantel-Haenszel procedure (Rothman & Boice 1979). The relative risk of dichotomous outcome variables for the prophylactic antibiotic group compared with the placebo group were calculated with corresponding 95% confidence intervals (CI) by the test-based method (Rothman & Boice 1979). In situations with small expected values in the numerator, we used an exact procedure (Thomas 1975).

Results

Women studied

We enrolled 1813 women: 904 were allocated to

Table 1. Characteristics of the women in the study

Characteristic	Prophylactic doxycycline (*n* = 827) Mean	Placebo (*n* = 828) Mean	Lost to follow-up (*n* = 158) Mean	*P**
Age (years)	25·5	25·3	25·6	0·51
Years of education	9·5	9·7	9·2	0·02
No of live births	2·5	2·3	2·4	0·03
No. of miscarriages	0·2	0·2	0·2	0·78
Coital frequency/week	2·4	2·4	2·5	0·48

* One-way analysis of variance on the three groups.

the prophylactic doxycycline group and 909 to the placebo group. Follow-up information was obtained from 91% in both groups. Our 1-month comparative analyses included those women for whom we had follow-up information: 827 in the prophylactic doxycycline group and 828 in the placebo group.

The treatment groups and those lost to follow-up were similar in terms of age, years of education, live births, miscarriages and coital frequency per week (Table 1). There were statistically significant but practically unimportant differences in years of education and live births. Marital status, type of IUCD inserted, and bacterial status before IUCD insertion were similar in the treatment groups (Table 2). No known perforations of the uterus occurred during the study, and an equal number of failed insertions occurred in each group. The only statistically significant difference in side-effects between the two groups was for vomiting which occurred in 4·8% of the doxycycline group, and in 1·9% of the placebo group ($P<0{\cdot}001$).

PID

Prophylactic antibiotics reduced the risk of PID. Overall, the PID rates were low, 1·3% in the doxycycline group and 1·9% in the placebo group (Table 3). The rate in the doxycycline group was 31% lower than in the placebo group ($P = 0{\cdot}17$), and the results changed negligibly when we adjusted for potential confounding factors such as education, parity, coital frequency, age, and previous type of contraceptive used. This reduction in PID in the group receiving doxycycline prophylaxis occurred primarily in the women without endocervical chlamydial infection. Those women in whom cultures for endocervical gonorrhoea and chlamydia were negative at insertion showed a 33% reduction in PID (Table 4). In women positive for gonorrhoea but negative for chlamydia, doxycycline produced a substantial protective effect, but small numbers led to some imprecision. However, in women positive for chlamydia only, doxycycline did not produce a substantial protective effect.

Doxycycline had a greater protective effect with the active IUCDs. We combined the results from the Copper T, Nova T and Multiload into an active IUCD category; in this category doxycycline produced a 78% reduction in PID [RR 0·22; 95% CI 0·03 to 1·5; $P = 0{\cdot}06$). With the Lippes loop, doxycycline produced only an 11% reduction (RR 0·89; 95% CI 0·38 to 2·1; $P = 0{\cdot}39$).

Unscheduled IUCD-related visits

Prophylactic antibiotics reduced the risk of problems leading to unplanned IUCD-related visits. The rate of return to the clinic for a problem related to the IUCD in the doxycycline

Table 2. Bacteriological status and types of IUCD in the two treatment groups

Characteristic	Prophylactic doxycycline (*n* = 827) (%)	Placebo (*n* = 828) (%)	Two-tailed *P*
Currently married	68·0	67·0	0·81
Lippes loop	82·2	80·2	0·35
Copper T	5·3	5·8	
Nova T	8·8	8·6	
Multiload	3·3	5·0	
Failed insertion	0·4	0·4	
Gonorrhoea positive	3·2	4·0	0·35
Chlamydia positive	12·9	12·0	0·59

Table 3. Rates and relative risks (RR) of the major outcomes for the first month after IUCD insertion by treatment group

Outcome	Prophylactic doxycycline ($n = 827$)	Placebo ($n = 828$)	RR	95% CI	One-tailed P
PID	1·3%	1·9%	0·69	(0·32 to 1·5)	0·17
Unplanned IUCD-related visit	8·9%	13·0%	0·69	(0·52 to 0·91)	0·004

PID, pelvic inflammatory disease; IUCD, intrauterine contraceptive device.

group was 31% lower ($P = 0{\cdot}004$) than in the placebo group, with a narrow confidence interval (Table 3). The results changed negligibly when we adjusted for potential confounding factors such as education, parity, coital frequency, age, and previous type of contraceptive used.

We reviewed the women's complaints for their unplanned IUCD-related visits: 66% were for lower abdominal pain, back pain, bleeding and/or vaginal discharge, with most women reporting at least two of those complaints, and 27% were related solely to expulsion or to the woman's concern about the position of the IUCD. Prophylactic doxycycline reduced the risk of an unscheduled visit for lower abdominal pain or bleeding by 41% (RR 0·59; 95% CI 0·39 to 0·89; $P = 0{\cdot}006$). The effect of doxycycline on unscheduled visits for the other complaints was less pronounced, a 21% reduction (RR 0·79; 95% CI 0·53 to 1·2; $P = 0{\cdot}12$).

When the unscheduled-visit rates were stratified by bacteriological findings at insertion, a similar picture to the PID results emerged. In women with cervical chlamydial infection there was no protective effect of doxycycline on unplanned visits. In women without any endocervical infection at insertion and in those positive for gonorrhoea but negative for chlamydia, doxycycline effected a 38% and 59% reduction, respectively, in the rates of unplanned IUCD-related visits (Table 5). In women with chlamydial infection the protective effect of doxycycline was negligible.

Discussion

In the present study the frequency of PID in women using IUCDs was much lower than expected from previous estimates in Kenya. The general belief was that the PID rate in IUCD users was about 10%. In retrospect, these high estimates of PID were presumably a reflection of experience with unscheduled IUCD-related visits, and not PID as defined in the present study. We planned conservatively for an incidence rate of 4% in the placebo group; the resultant rate was <2% thus lessening the power of the trial to demonstrate a difference. The magnitude of our error is perhaps not surprising since that has been no other completed study of PID incidence in Africa. The fact that we found much lower incidence rates of PID is detrimental to study power, but is reassuring in terms of the safety of IUCD use in Kenya.

Table 4. Rates and relative risks (RR) of pelvic inflammatory disease (PID) for the first month by bacteriological status at the time of IUCD insertion and by treatment group

Bacteriological status	PID rate: Prophylactic doxycycline	PID rate: Placebo	RR	95% CI	One-tailed P
Neither gonorrhoea nor chlamydia	0·90% ($n = 669$)	1·3% ($n = 670$)	0·67	0·24 to 1·9	0·22
Gonorrhoea only	0·0% ($n = 19$)	11·1% ($n = 27$)	0·00	0·00 to 2·3	0·19
Chlamydia only	2·1% ($n = 96$)	2·2% ($n = 90$)	0·94	0·07 to 12·7	0·67

* This table does not include the results of 73 women who were not tested for gonorrhoea and chlamydia and 11 women who were positive for both chlamydia and gonorrhoea.

Table 5. Rates and relative risks (RR) of unplanned IUCD-related visits for the first month by bacteriological status at the time of IUCD insertion and by treatment group

	Unplanned visit rate				
Bacteriological status	Prophylactic doxycycline	Placebo	RR	95% CI	One-tailed *P*
Neither gonorrhoea nor chlamydia	8·1% (*n* = 669)	13·0% (*n* = 670)	0·62	0·45 to 0·86	0·002
Gonorrhoea only	10·5% (*n* = 19)	25·9% (*n* = 27)	0·41	0·10 to 1·7	0·10
Chlamydia only	10·4% (*n* = 96)	11·1% (*n* = 90)	0·94	0·41 to 2·1	0·44

* This table does not include the results of 73 women who were not tested for gonorrhoea or chlamydia and 11 women who were positive for both gonorrhoea and chlamydia.

Clinical criteria for diagnosing PID are not well established or uniform. Even in experienced hands, the predictive value of a positive diagnosis may be as low as 0·65 (Jacobson & Westrom 1969), which means that one in three patients admitted with a diagnosis of PID does not have this disease as judged by laparoscopy. Hence, we chose to use a rigorous case definition of PID (Hager *et al.* 1983). PID was sought using these criteria at each follow-up visit, both scheduled and unscheduled. By using a strict case definition, we believe we minimized the possibility of cramping related to the IUCD being misdiagnosed as PID. Using a less strict case definition, however, such as unplanned IUCD-related visits, leads to similar but statistically stronger conclusions.

Our results showed that a single oral dose of doxycycline at the time of insertion reduces the likelihood of PID by 31%. Whilst the alpha error of 0·17 does not meet the conventional standard of 0·05, the observed reduction in PID is consistent with current knowledge and our results for unplanned IUCD-related visits. That prophylactic doxycycline would reduce the likelihood of PID is biologically plausible. Moreover, in this study, the similar reduction found for unplanned IUCD-related visits was strongly statistically significant and corroborates the reduction found for PID. Of these visits, prophylactic doxycycline reduced those for lower abdominal pain or bleeding by 41%, and both have been associated with histological evidence of acute and chronic endometritis (Ober *et al.* 1968, 1970). Hence, the statistically significant reduction in the frequency of clinic visits is probably due largely to a reduction in the occurrence of endometritis in the group receiving prophylaxis. These findings are consistent with the effect of prophylactic antibiotic administration for induced abortion (Grimes *et al.* 1984; Park *et al.* 1985). In the largest study of prophylactic antibiotics for induced abortion, minor side-effects such as cramping and bleeding were consistently reduced in the group receiving tetracycline (Hodgson *et al.* 1975). Thus, this study suggests that antibiotic prophylaxis protects against both endometritis and salpingitis.

The stratified analyses by cervical culture results were pre-specified but, nonetheless, are intended primarily for hypothesis generation. The benefit of prophylaxis appears evident for women whose cervical cultures were negative for both *N. gonorrhoea* and chlamydia at the time of insertion, but the benefit appeared to be greatest for women with cervical gonorrhoea whereas doxycycline had little benefit for women with cervical infection with *C. trachomatis*. These findings might seem paradoxical, since doxycycline is a drug of choice for treating *C. trachomatis* infection but not for treating gonorrhoea (Centers for Disease Control 1985). These differential effects of prophylaxis probably stem from the different rates of growth of these pathogens. The gonococcus replicates in a matter of hours, compared with several days for *C. trachomatis* (Thompson & Washington 1983). Therapeutic levels of a single 200 mg dose of doxycycline would be present in the endometrium during several life-cycles of the gonococcus as compared with a fraction of that for *C. trachomatis*. Thus, the lack of benefit seen among women infected with *C. trachomatis* probably represents inadequate duration of therapeutic levels of doxycycline.

Ideally, an IUCD should not be inserted in women with gonorrhoea or cervical infection with *C. trachomatis.* To accomplish this, however, all women would have to be screened for these infections at an earlier visit, and those with infections adequately treated. Unfortunately, in countries where health care resources are overextended, resources that can reasonably be put into identifying women at risk of PID are limited. The additional clinic visit would impose extra costs and inconvenience that in most cases neither the woman nor the clinic would be willing to accept. Furthermore, even if screening were implemented, if a woman had negative tests for these pathogens, she might be infected at the time of IUCD insertion because of false-negative tests or acquisition of infection in the interval between screening and insertion. Moreover, women without either of these cervical infections appear to benefit from prophylactic doxycycline. Hence, the routine use of prophylaxis for all women receiving IUCDs needs to be considered as a practical alternative.

The use of prophylactic doxycycline may not only reduce human suffering and free encumbered health care resources, but may provide cost-savings as well. The cost of prophylaxis is low. When purchased in large quantities, the wholesale price of doxycycline is about $0·05 for a 100 mg tablet or capsule (*Drug Topics Red Book* 1988). Assuming that a 200 mg dose costs $0·10, then prophylactic treatment of 1000 women receiving an IUCD would cost $100 and might avert six cases of PID and 41 problems requiring an unscheduled IUCD-related visit to the clinic. Nearly all patients in the study with PID were admitted to hospital, but the proportion of patients with PID who were admitted may not be capable of extrapolation to other Kenyan women. However, when one considers the direct medical cost of six ambulatory or admitted women with PID and 41 problems requiring unplanned clinic visits, the figure would greatly exceed $100. The averted costs of ectopic pregnancy, infertility, and lost productivity would make prophylaxis even more cost-effective (Washington *et al.* 1986). In lower risk populations, such as the UK, the number of averted cases and visits per 1000 women would be fewer. Treatment costs, however, are much higher, and the savings would be greater. As has been shown for prophylaxis for suction curettage abortion, use of antibiotics is cost-effective even when the risk of infectious morbidity is lower than 1% (Grimes *et al.* 1984).

In summary, the prophylactic use of doxycycline at the time of IUCD insertion appears effective, well tolerated, and cost-effective. Because of the potential importance of this observation, corroboration by other studies is needed. One such trial is currently in progress in Nigeria using the identical protocol to this study (P. Lamptey, personal communication). Also, the advisability of giving more than one dose of doxycycline to prevent chlamydial PID should be investigated. Prophylactic antibiotic administration may make intrauterine contraception an even safer option in the years ahead.

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Anaesthesia for emergency caesarean section

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Summary. The Report on Confidential Enquiries into Maternal Deaths in England and Wales 1982–84 (Department of Health 1989) recommends early involvement of the anaesthetist in women having emergency caesarean sections and the use of epidural anaesthesia in preference to general anaesthesia. In an observational prospective study the need for emergency abdominal delivery could be anticipated in 87% of 360 consecutive emergency caesarean sections. Early establishment of epidural analgesia allowed extension, to an appropriate level for the surgery, in 70%. The duty anaesthetist accompanying the obstetric team on three wardrounds a day could be forewarned of anticipated problems in most women who are eventually delivered abdominally.

Appraisal of the feasibility of improving preoperative assessment and the provision of epidural anaesthesia was one objective of a prospective study of emergency caesarean sections. Such improvements are limited by the quantity and quality of anaesthetic manpower available, given the very large number of obstetric units requiring anaesthetic services and the competing needs of other surgical disciplines (Morgan 1987).

Minor organizational changes that allow early involvement of the anaesthetist with the women in labour could increase maternal safety.

Subjects and methods

A prospective observational study of 360 consecutive patients delivered by emergency caesarean section was undertaken to assess a policy of recommending epidural analgesia early in labour in circumstances where a strong possibility of eventual delivery by caesarean section was suspected.

Epidural analgesia was recommended for women who seemed likely to require abdominal delivery because progress in labour was delayed in spite of augmentation with oxytocin or because of abnormal fetal cardiotocography, or when fetal blood sampling was considered necessary. It was also recommended for women with breech presentation, non-engaged fetal head or persistent occipito-posterior position, twin pregnancy, suspected intrauterine growth retardation and trial labour in the presence of suspected cephalopelvic disproportion or a uterine scar. Pre-eclamptic patients were encouraged to have epidural blocks for emergency caesarean section, whether or not they were in labour, provided coagulation defect had been excluded. This policy provided time for the epidural block to be established and for efficacy of the block to be demonstrated, allowing timely extension for surgical anaesthesia, if necessary.

When the decision to perform a caesarean section was taken the obstetrician indicated the degree of urgency in terms of a proposed decision to delivery time (PDDT) interval of <10 min, 11–30 min or >30 min, as well as the

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reasons for the operation. The anaesthetist recorded the condition of the patient and the fetus, the duration of labour, type of anaesthetic given, relevant time intervals and complications of anaesthesia. The presence or absence of the partner at the birth and whether or not the mother held the baby immediately after delivery were also noted.

The duty paediatrician recorded the gestational age, Apgar scores and time to sustained respiration of the newborn infant.

Statistical comparisons were made by the χ^2 and Student's *t*-test. A *P* value of $<0{\cdot}05$ was regarded as significant.

Results

Among the 360 consecutive emergency caesarean sections there were no signs of fetal distress in 223 (62%). The indications for the caesarean sections, the number (%) with and without fetal distress are given in Table 1. Fetal distress was a factor in 137 (38%) of the patients. In 89 (25%) fetal distress was the decisive factor in addition to other risk factors. Table 2 shows the proposed decision-to-delivery-time (PDDT) in minutes in pregnancies with fetal distress (with and without other risk factors) as well as those with no fetal distress. Only 48 (13%) women had emergency caesarean sections for fetal distress with no other earlier warning signs. In these patients the need for caesarean section could not have been anticipated, but in all the others the decision to carry out a caesarean section was not unexpected.

Only 78 (22%) of the women in the study spent less than 4 h in hospital before the emergency caesarean section. Fifty-one (14%) were not in labour but had been admitted with antenatal complications, mainly pregnancy-induced hypertension. Some had been transferred from other hospitals in the interest of infants who may have required neonatal intensive care facilities.

Assessment of the women by the obstetrician, midwife and anaesthetist early in labour allowed timely administration of an epidural block to those who seemed likely to require abdominal delivery. This permitted 251 (70%) of them to have their caesarean section under epidural block (Table 3). There were 27 women (7%) who, in spite of receiving an epidural block in labour, had a general anaesthetic for the operation and 80 (22%) who did not have epidural analgesia for labour had general anaesthesia for surgery.

In 194 (77%) of those having the section under epidural, the block was already established. In 56 of these patients fetal distress was present and the mean time from induction to adequate block was 16·17 (SD 10·54) min. In this group 47 patients had an induction-to-adequate-block interval of <10 min. In the less urgent cases where the block was initiated after the decision to operate, more time was required and in one instance 80 min elapsed from the start of epidural to delivery. The induction-to-delivery interval with epidural anaesthesia is often longer than the time taken to achieve an adequate block because the operation may be delayed for reasons other than the anaesthetic. Thus overall in the epidural group the mean induction-to-delivery interval was 31·6 (SD 14·5) min but the mean time from induction to adequate block was 17·9 (SD 10·1) min. The mean incision-to-delivery time in the epidural group (7·03 SD 3·7 min) was slightly longer than in the general anaesthesia group (mean 5·07

Table 1. Indications for caesarean section and numbers (%) with and without fetal distress

Indication for caesarean section	No fetal distress	(%)*	Fetal distress	(%)*
No progress	112	(31)	38	(11)
No progress plus maternal pyrexia	15	(4)		
No progress in trial of scar	54	(15)		
Malpresentation and multiple pregnancy	20	(6)	12	(3)
Pre-eclampsia	22	(6)	22	(6)
Suspected intrauterine growth retardation			17	(5)
Fetal distress alone			39	(11)
Cord prolapse			4	(1)
Placental abruption			5	(1)
Total	223	(62)	137	(38)

* Percentage of all 360 caesarean sections.

Table 2. Proposed decision-to-delivery-time (PDDT) in pregnancies with and without fetal distress and other risk factors

	Fetal distress			
PDDT (min)	Present	Present plus other risk factors	Absent	Total
<10	31	14	6	51
11–30	15	43	73	131
>30	2	32	130	164
Not stated			14	14
Total	48	89	223	360

SD 2·7 min) ($P<0{\cdot}001$). The times from uterine incision to delivery and incision to end of operation did not differ significantly between epidural and general anaesthesia.

Overall 205 (57%) of the study group were primiparae and significantly more primiparae than multiparae had epidural anaesthesia: 127 (62%) vs. 59 (38%) ($P<0{\cdot}0002$).

Fetal distress had been diagnosed in a third of the women sectioned under epidural block, in just over half of these sectioned under general anaesthesia and in three quarters of those who had both epidural analgesia and general anaesthesia.

There was no significant difference in the neonatal condition of the 307 infants born at >35 weeks gestation between those in the epidural group and those in the general anaesthesia group. Fewer babies born with general anaesthesia had a 1 min Apgar score >8 (34 (47%) vs. 147 (63%) $P<0{\cdot}005$) but this is probably not clinically important.

There were 47 infants born at <35 weeks gestation and these showed no significant difference in neonatal condition related to the type of anaesthesia. Endotracheal intubation was required in 31% of the infants in the epidural group and 59% in the general anaesthesia groups. The paediatric details were not recorded for six infants.

Of the 256 mothers who were awake for the birth 203 held the child immediately; 145 fathers were present at the birth under epidural anaesthesia but only five where the mother was unconscious.

Discussion

There was sufficient time for the anaesthetist to see and assess preoperatively most women who required emergency caesarean section. Involvement of the duty anaesthetist in formal ward-rounds at 09.00 hours, 17.00 hours and midnight does not add an intolerable burden to the anaesthetist's schedule but may add considerably to maternal safety. Almost 90% of women delivered by emergency caesarean section had

Table 3. Type of anaesthesia and urgency to delivery

	Proposed decision-to-delivery-time (min)				Total	
Anaesthesia	<10	11–30	>30	Not stated	*n*	(%)
Effective epidural established	12	93	79	10	194	(54)
Epidural inserted for caesarean section	0	6	49	2	57	(16)
Spinal	0	1	1	—	2	
General anaesthesia						
With ineffective epidural	4	4	7	—	15	(4)
With effective epidural	7	1	4	—	12	(3)
No epidural	28	26	24	2	80	(22)
Numbers of patients	51	131	164	14	360	

earlier indications that abdominal delivery was a likely outcome.

Pre-operative assessment is particularly important in the 65% of British obstetric units in which an anaesthetist is shared between obstetrics and other disciplines, either in the same hospital or on other site (Morgan 1987). It allows the anaesthetist to avoid having to administer a rushed general anaesthetic to a high risk patient whom he has never seen before with inadequate time to assess the risks that she may present.

The Confidential Enquiry into Perioperative Deaths (CEPOD) (Buck *et al.* 1987) states that 'pre-operative assessment by the patient's anaesthetist is an integral part of the practice of anaesthesia; omission of this in nearly 10% of the cases suggests a defect in attitude and organisation'. There is no justification for adopting a lower standard of anaesthetic care for obstetric than for surgical patients.

The prevailing anaesthetic view (Corall 1982) is that in emergency caesarean section there is no possibility of such assessment as most cases are unforeseen and extremely urgent, necessitating great hurry. These views can no longer be endorsed. There is no excuse for the anaesthetist, even with shared duties, failing to undertake wardrounds of women in labour with the obstetric team of which he should be an integral part (RCOG Working Party 1982). There is also little excuse for the obstetrician failing to inform the anaesthetist of a possible impending abdominal delivery and thus allow time for proper assessment of the patient.

The problem of the sudden unexpected very acute emergency certainly exists, but such occurrences are unusual. In this study group 48 (13%) of infants needed abdominal delivery with no prior warning, and 31 of them needed immediate delivery. Delay could have led to hypoxic cerebral damage in some of these infants. However, haste is a recognized factor in critical anaesthetic incidents (Craig and Wilson 1981, Cooper 1978) and should not be allowed to endanger the pregnant woman, especially as the diagnosis of fetal distress may be incorrect (Sykes *et al.* 1983).

Davis (1982) calculated that with use of subarachnoid and epidural block, general anaesthesia would only be required for this operation in 16% of patients. Other authors have reported figures as low as 3.5% for general anaesthesia (Sosis and Bodner 1983).

Some clinicians consider epidural anaesthesia unsuitable for caesarean section unless there is no limitation of time, but this objection does not apply if the block is already established at the time of operation and is effective.

Epidural block for caesarean section virtually eliminates the risk of aspiration of gastric contents and failed intubation, the two commonest anaesthetic causes of maternal death and may also reduce the risk of pulmonary embolism (Perhoniemi and Linko 1987, Modig *et al.* 1980, Poikeleninen and Hendolin 1983) which causes 17% of maternal deaths after caesarean section (Department of Health 1989, p. 89). Reduced maternal post-operative morbidity (Morgan *et al.* 1984) and improved condition of the newborn infant following fetal hypoxia (Marx *et al.* 1984) are further advantages of conduction block anaesthesia. Psychological benefit may also accrue to the parents.

It is possibly the greatest advantage of epidural anaesthesia that it allows anaesthetic preparation for emergency caesarean section without the decision to operate having first been taken.

Complications of general anaesthesia were less common but more serious; one patient was difficult to intubate, one developed severe bronchospasm following the muscle relaxant and one was aware during surgery. In contrast, epidural anaesthesia was associated with more complications but none of these was life threatening. Of the 251 women 22 (9%) complained of pain during surgery that was treated in most cases with entonox or opiates, or both, with satisfactory response. Hypotension, defined as a fall in systolic blood pressure to at least 20% below the initial level, or <100 mmHg, occurred in 44 (18%) and was treated with intravenous fluid infusion, supplemented in 41 of these with ephedrine administration. Nausea occurred in 49 (20%) and vomiting in 12 (5%). Twelve women complained of paraesthesia of fingers indicating a high block.

Spinal anaesthesia was used in only two women which represents the lack of confidence of the duty anaesthetists in this anaesthetic technique rather than its true potential in the circumstances described. Its role may increase as more anaesthetists become proficient at using the technique for elective caesarean section.

Fetal distress requiring immediate delivery is the most important indication for general anaesthesia. This is the most rapid and certain anaesthetic technique available but it was only necessary in 13% of the emergency caesarean sections in this study.

The Report on Confidential Enquiries into Maternal Deaths in England and Wales 1982–82 (Department of Health 1989, p. 95) recommends early involvement of the duty anaesthetist and the preferred use of epidural rather than general anaesthesia, where possible for emergency caesarean sections. Meeting these recommendations is facilitated by the duty anaesthetist's participation, with other members of the obstetric team, in routine labour ward rounds at designated times.

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Blood flow velocity waveforms from the fetal external iliac artery as a measure of lower extremity vascular resistance

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Summary. Blood flow velocities were recorded in the external iliac artery (EIA) and umbilical artery (UA) in 94 normal pregnancies and in 14 with intrauterine growth retardation (IUGR) between 25 and 36 weeks gestation. In normal pregnancy the pulsatility index (PI) in both vessels decreased significantly with advancing gestational age, reflecting a reduction in lower extremity and placental vascular resistance. The EIA PI/UA PI ratio also decreased significantly with gestational age suggesting that vascular resistance is more pronounced in the lower extremities. In the pregnancies with IUGR, PI values from both vessels were nearly always above the upper limit (+2 SD) of the normal curve reflecting increased vascular resistance at lower extremity and placental level. In two pregnancies, absent end-diastolic flow velocities in the umbilical artery were associated with reversed end-diastolic flow velocities in the external iliac artery.

Analysis of blood flow velocity waveforms from the fetal descending aorta, umbilical artery and internal carotid artery suggests that also in the growth-retarded human fetus, chronic hypoxaemia is associated with a raised vascular resistance at fetal trunk and placental level (Campbell *et al.* 1983; Griffin *et al.* 1984; Wladimiroff *et al.* 1986). If centralization of the circulation indeed occurs, one may expect the vascular resistance at lower extremity level to be raised as well.

In this communication we introduce a pulsed Doppler method for recording the flow velocity waveform in the external iliac artery in the human fetus and compare this flow velocity waveform with that obtained in the umbilical artery.

Subjects and methods

A Sonotron Vingmed CFM 700 mechanical sector scanner (carrier frequency 5 MHz, Doppler 4 MHz or carrier frequency 3 MHz, Doppler 3 MHz with variable depth of sample gate and sample size) was used to identify the fetal external iliac artery. This vessel was easily identified using colour-coded Doppler techniques. In colour-coded Doppler systems the Doppler shift is displayed in real-time, colour encoded, with red indicating flow towards the transducer and blue flow away from the transducer. Thus, regardless of fetal position, it is possible to identify direction of flow in specific vessels unequivocally. First, the fetal bladder was identified and

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the transducer placed in a longitudinal or slightly oblique axis. The most distal portion of the fetal bladder, just above the genitalia, was brought into view. Clearly pulsating vessels were readily identified in this region. Precise placement of the sample volume was facilitated by switching to colour mode whereby a differentiation could be made between the external iliac artery and the intra-abdominal umbilical artery. Although these vessels are very close to one another (Fig. 1) colour-coded flow mapping clearly identified flow direction towards the fetal legs (i.e. external iliac artery) and flow away from the legs (i.e. intra-abdominal umbilical artery). Following identification of the external iliac artery, the maximum flow velocity waveform was recorded (Fig. 2) on hard copy. The maximum flow velocity waveform in the umbilical artery (cord section) was obtained according to the method first described by McCallum *et al.* (1978) and also documented on hard copy. All measurements were made under an angle of less than 20° between transducer and vessel. The degree of pulsatility of both waveforms was quantified by calculating the pulsatility index (PI) according to Gosling & King (1975) using an Apple III micro computer. Each measurement included an average of four consecutive cycles and was made during fetal apnoea.

A total of 103 normal pregnant women between 18 and 38 weeks gestation consented to participate in the study. In nine subjects we failed to obtain a satisfactory flow velocity waveform in the external iliac artery due to maternal obesity or excessive fetal motility, leaving 94 pregnancies for further assessment. Birthweights were between the 10th and 90th centile for gestational age according to the Tables published by Kloosterman (1970) corrected for maternal parity and fetal sex.

We have investigated 14 pregnancies complicated by intrauterine growth-retardation (IUGR) at between 25 and 36 weeks gestation. IUGR was defined by: (i) flattening of the growth pattern resulting in a clinical discrepancy of >2 weeks of fundal height on two successive appointments combined with an upper abdominal circumference ultrasound measurement <5th centile in association with normal or reduced head circumference measurement (Campbell 1976); (ii) postnatal confirmation by birthweight <5th centile for gestational age (Kloosterman 1970).

Statistical analysis of normal pregnancies

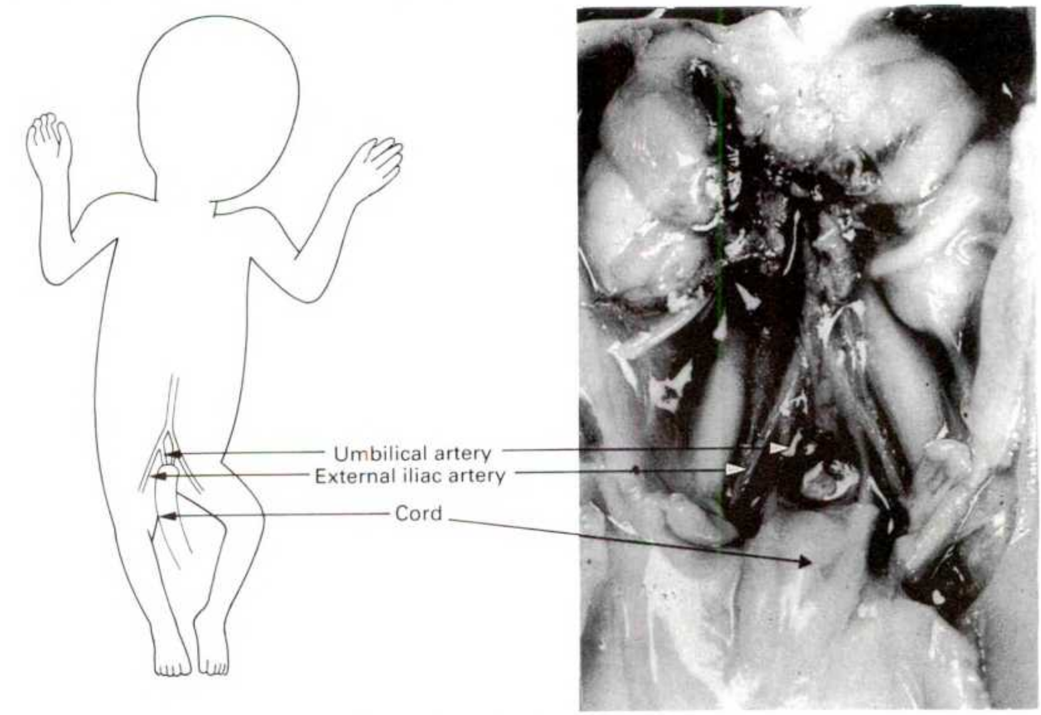

Fig. 1. Post mortem and schematic image of the anatomic relationship between external iliac and umbilical artery at the level of flow velocity waveform recording.

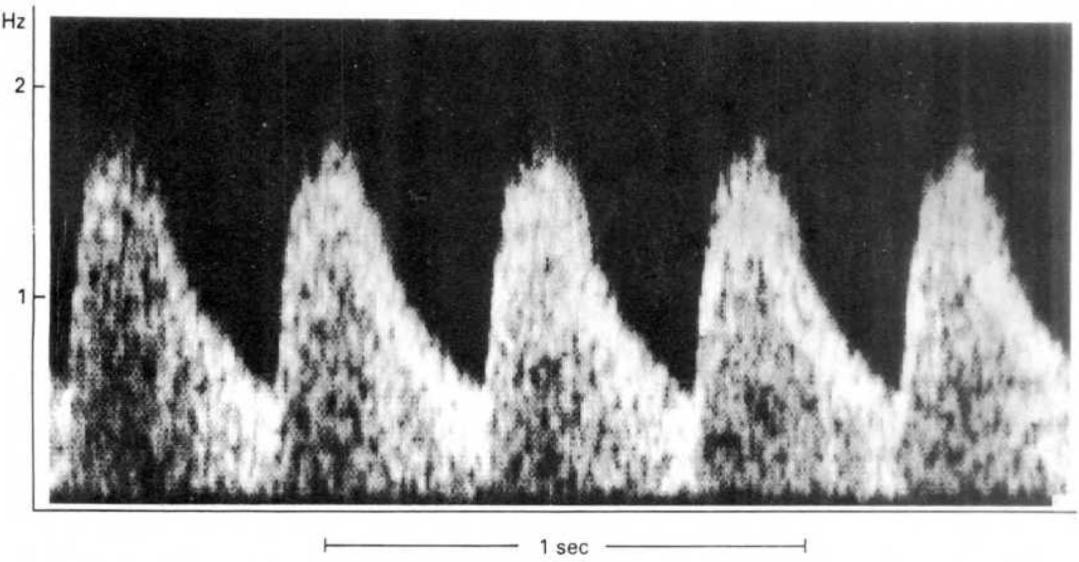

Fig. 2. Flow velocity waveform from the external iliac artery in normal pregnancy at 30 weeks gestation. Note the presence of forward flow throughout the cardiac cycle.

included investigations of the relation between the PI values from the external iliac artery (EIA PI) and from the umbilical artery (UA PI) and gestational age by linear regression analysis. The relation between the EIA PI/UA PI ratio and gestational age was also established.

Results

During normal pregnancy, there is continuous forward flow throughout the cardiac cycle in the external iliac artery (Fig. 2). The mean EIA PI and mean UA PI could be described by a linear function of gestational age (Figs. 3 and 4), the EIA PI/UA PI ratio by a quadratic function of gestational age (Fig. 5). The regression equations for EIA PI and UA PI are given by $\text{EIA PI} = -0{\cdot}0347\times\text{AGE}+2{\cdot}219$ and $\text{UA PI} = -0{\cdot}0259\times\text{AGE}+1{\cdot}825$. The slopes of these lines are highly significant ($P<0{\cdot}001$). The regression curve for the EIA PI/UA PI ratio is given by $\text{EIA PI/UA PI ratio} = -0{\cdot}00079\times\text{AGE}^2+0{\cdot}0394\times\text{AGE}+0{\cdot}686$. The regression coefficients in this equation differ significantly from zero ($P<0{\cdot}01$).

The PI values for the IUGR group (Table 1) were compared with the upper limit (mean +2 SD) of the PI values for the normal population. Increased values were established in all pregnancies with IUGR for the EIA PI (100%) and in most of them for the UA PI (93%). Raised EIA PI/UA PI ratio values were established in only 14% of growth-retarded fetuses.

Discussion

Flow velocity waveforms were successfully obtained from the fetal external iliac artery in 91%. The femoral artery would have been a more obvious choice for assessing lower extremity blood flow. However, despite colour coded Doppler, we only rarely succeeded in identifying this particular vessel. The principal reason is the closely related course of the femoral artery and femur, thus often concealing the vessel from ultrasound inspection.

Forward flow in the external iliac artery throughout the cardiac cycle in normal pregnancy reflects low fetal vascular resistance as has also been established from other fetal vessels (Griffin *et al.* 1984; Trudinger *et al.* 1985; Reuwer *et al.* 1987; Wladimiroff *et al.* 1988). PI in the external iliac artery decreases with advancing gestational age indicating a reduction in lower extremity vascular resistance during the second half of gestation. The decline in EIA PI/UA PI ratio with advancing age suggests that in the lower extremities decrease in vascular resistance is more pronounced than in the umbilical artery. Of interest is that volume flow measurements in the descending aorta and umbilical vein during the third trimester (Lingman *et al.* 1986) suggest an increase in volume flow to the lower extremities relative to placental blood flow.

In IUGR, virtually all PI values from the umbilical artery were situated above the upper

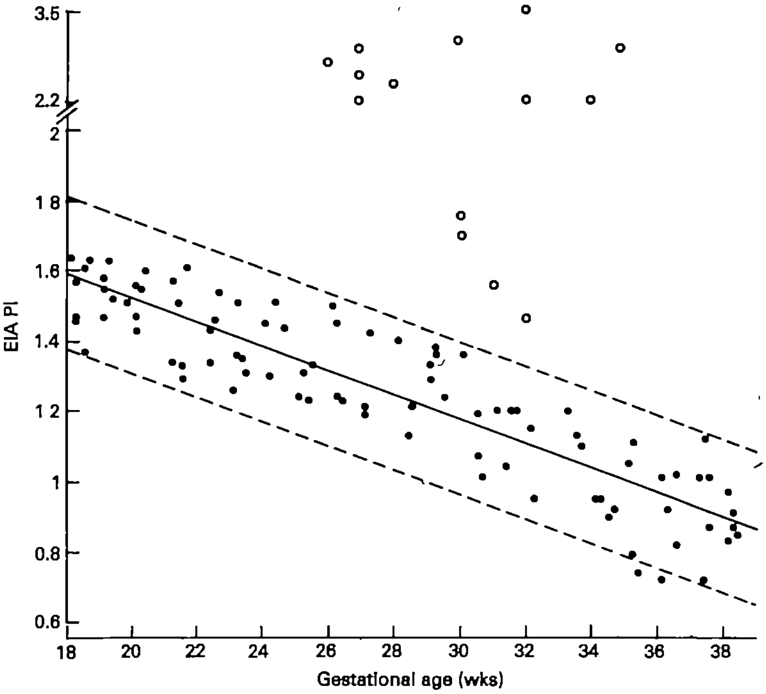

Fig. 3. Mean (±2 SD) for the pulsatility index (PI) from the external iliac artery (EIA) in normal pregnancy. The closed circles denote normal pregnancy ($n = 94$), the open circles represent IUGR ($n = 14$).

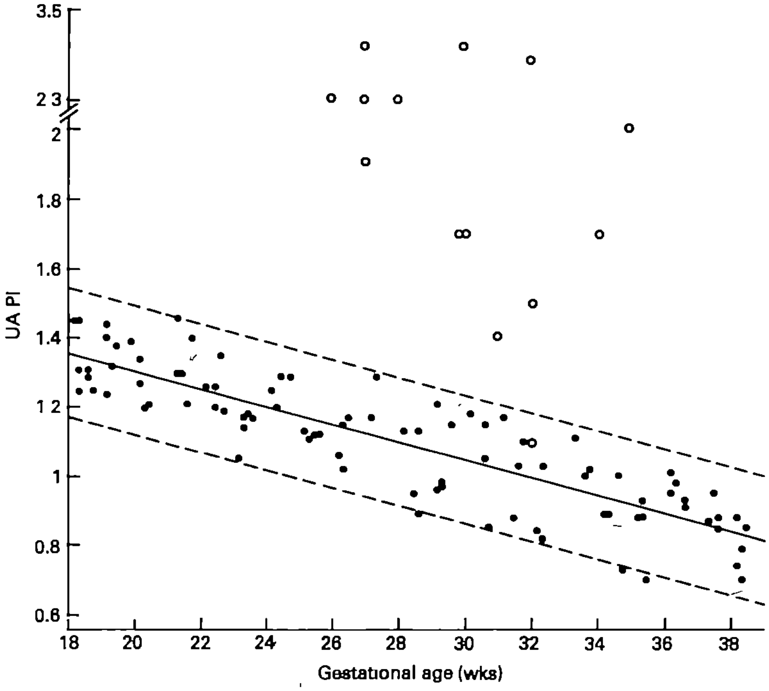

Fig. 4. Mean (±2 SD) for the pulsatility index (PI) from the umbilical artery (UA) in normal pregnancy. The closed circles denote normal pregnancy ($n = 94$), the open circles represent IUGR ($n = 14$).

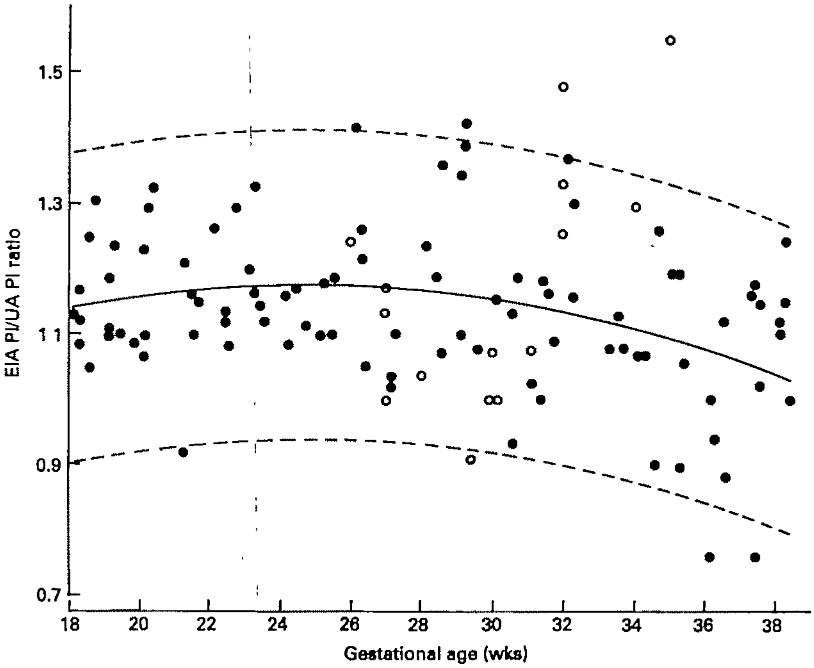

Fig. 5. Mean (±2 SD) for the pulsatility index (PI) for the EIA PI/UA PI ratio in normal pregnancy The closed circles denote normal pregnancy ($n = 94$), the open circles represent IUGR ($n = 14$)

limit of the normal curve reflecting raised placental vascular resistance and impaired placental perfusion. PI values from the external iliac artery were also elevated, indicating increased vascular resistance at lower extremity level in IUGR. The rise in PI in both vessels was not essentially different, as is demonstrated by the EIA PI/UA PI ratio values. In two pregnancies raised ratios were recorded at 32 and 35 weeks respectively. In both instances absent end-diastolic flow velocities in the umbilical artery were associated with reverse flow velocities in the external iliac artery. Both fetuses displayed an abnormal heart rate pattern 24 to 48 h later, necessitating birth by caesarean section; the Apgar scores were 6 and 7 at 1 min, and the umbilical cord pH values were 7·15 and 7·13. Long time intervals between flow recording and delivery did not allow comparison with the outcome in other infants. A different study design is needed to establish the possible clinical significance of this observation.

Finally, data from the present study are consistent with previous data that also in the human fetus impaired placental perfusion appears to be associated with circulatory centralization as expressed by a raised vascular resistance at fetal trunk, low extremity and placental level and a reduced vascular resistance at cerebral level, suggesting a brain-sparing effect.

Table 1. The pulsatility index from the external iliac artery (EIA) and umbilical artery (UA) and for the external iliac artery/umbilical artery ratio (EIA PI/UA PI ratio) in 14 pregnancies with intrauterine growth retardation

Subject no.	Gestational age (weeks)	Pulsatility index		
		EIA	UA	EIA/UA ratio
1	26	2·8	2·2	1·2
2	27	3·0	3·0	1·0
3	27	2·6	2·3	1·1
4	27	2·2	1·9	1·2
5	28	2·4	2·3	1·0
6	30	3·1	2·9	1·1
7	30	1·7	1·7	1·0
8	30	1·8	1·7	1·0
9	31	1·5	1·4	1·1
10	32	2·2	1·5	1·5
11	32	1·4	1·1	1·3
12	32	3·5	2·8	1·2
13	34	2·2	1·7	1·3
14	35	3·1	2·0	1·6

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Uterine artery Doppler in the investigatioin of pregnancies with raised maternal serum alpha-fetoprotein

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Summary. Uterine artery flow velocity waveforms (FVW) were obtained prospectively by continuous wave Doppler at 18–22 weeks gestation from 98 women with an unexplained elevation in maternal serum alpha-fetoprotein (MSAFP). A notch in either the left or right uterine artery FVW was present in 18 pregnancies of which seven resulted in perinatal death and six in the birth of very immature and/or severely growth retarded babies. Conversely, in 66 of 80 pregnancies the absence of a notch was associated with the livebirth of an infant beyond 32 weeks gestation, with a birthweight above the 5th centile. It is suggested that the presence of a notch in the uterine artery FVW is a good predictor of poor perinatal outcome.

Measurement of maternal serum alpha-fetoprotein (MSAFP) is an established screening method for neural-tube defects (NTD) (UK Collaborative Study 1977). More recent emphasis on low MSAFP has resulted in its use for the prediction of trisomy 21 (Schoenfeld *et al.* 1987) A third possible use for MSAFP has arisen from reports that high levels in the absence of fetal malformations, incorrect dating, and multiple pregnancies are associated with an increased risk of perinatal death, preterm delivery and intrauterine growth retardation (IUGR) The reported perinatal mortality is 3·5–16·7%, while the rate for low birthweight (<10th centile) is as high as 33·3% and that for preterm (<37 weeks) delivery as high as 26% (Table 1) (Hamilton *et al.* 1985; Gordon *et al.* 1978; Wald *et al.* 1977; Legge *et al.* 1985; Mwambingu 1985).

Perinatal death, IUGR, and immaturity have also been associated with abnormal Doppler uterine artery flow velocity waveforms (FVW) (Campbell *et al.* 1983, 1986; Fleischer *et al.* 1986). In this study we investigated both the uterine artery resistance index (RI) and the presence or absence of an early diastolic notch on the uterine artery FVW for their ability to predict poor perinatal outcome in pregnancies with an unexplained elevation of MSAFP.

Patients and methods

Uterine artery FVW were obtained prospectively by continuous-wave Doppler at 18–22 weeks gestation from 98 women with elevated MSAFP levels and in whom detailed ultrasound scans had shown singleton fetuses with no malformations. All the women were referred from other hospitals for ultrasound examination because the 16-week MSAFP level, as determined by their reference ranges, was >2·5

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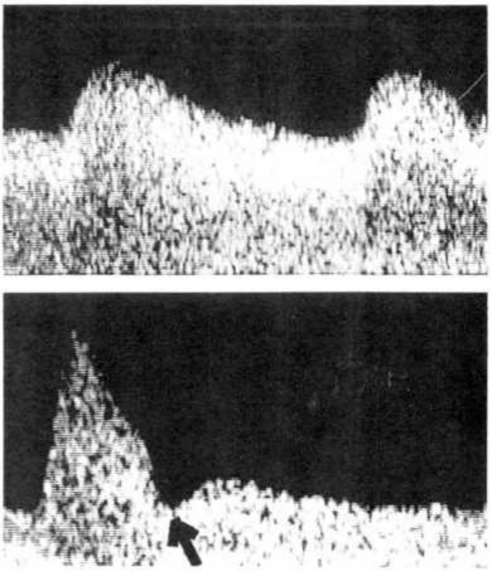

Fig. 1. Flow velocity waveform of the uterine artery from a normal pregnancy (top) and one with unexplained elevation of maternal serum alpha-fetoprotein (bottom); in the latter there is a notch in early diastole (arrow).

multiples of the median (MoM). The exact level of MSAFP and the extent of further local preselection of the women could not be defined. Gestational age was determined from the menstrual data and confirmed by ultrasound measurements at the referring hospitals.

In our unit the maternal height and weight were measured and an ultrasound examination was performed for exclusion of fetal malformations, assessment of amniotic fluid volume, and fetal biometry. Oligohydramnios was diagnosed when the largest measurable vertical pool of fluid was $\leqslant 2$ cm.

With the woman in the semi-recumbent position, the uterine artery FVW was recorded by an experienced operator using continuous-wave Doppler (Doptek Ltd, Chichester, UK). Characteristic FVW were recorded from both the right and left uterine arteries by directing the transducer along the lateral wall of the uterus at a level 2–3 cm below the anterior superior iliac spine. The presence or absence of a notch was noted (Fig. 1), and the RI (peak systolic frequency − end diastolic frequency/peak systolic frequency) was calculated and the highest value recorded.

Of the 98 women scanned at 18–22 weeks, 53 had further Doppler studies at 24–26 weeks gestation. These women were unselected as they were not informed of the Doppler findings and returned only if it was convenient. Likewise, the results of the Doppler studies were not given to the managing obstetricians. The gestational age at delivery, infant survival, birthweight and gender were obtained from the referring hospitals and were used, together with maternal height, weight, and parity data, to calculate the birthweight centile (Altman & Coles 1980).

Additionally, 85 pregnant women were recruited from the King's College Hospital antenatal clinic to form a reference range for uterine artery RI values at 18–22 weeks gestation. In each woman both uterine arteries were examined and the highest RI was used for further analysis. Inclusion criteria were a normal MSAFP level and an ultrasound scan showing a normal singleton pregnancy. Of these 85 pregnancies, 79 ended in normal term deliveries and from this group a normal reference range (mean and 95% CI) was generated.

In the normal pregnancies, regression analysis was used to describe the association between uterine artery RI and gestation. In the pregnancies with raised MSAFP, data were analysed using contingency tables, and the predictive ability of the uterine artery notch to detect any of the complications was calculated in terms of the sensitivity, specificity, and predictive values of a positive and negative test. Fisher's exact test was used to estimate the significance of any association between poor outcome and the presence of a uterine artery notch for the 98 women examined at 18–22 weeks gestation and for the subgroup of 53 women who were studied again at 24–26 weeks gestation.

Results

Normal pregnancies

In the 79 normal pregnancies with term deliveries of appropriate-for-gestational-age infants, the uterine artery RI decreased significantly with gestation ($n = 79$, $r = -0{\cdot}226$, $P<0{\cdot}05$, constant $= 1{\cdot}105$, slope $= -0{\cdot}024$, residual SD $= 0{\cdot}114$), in five of the records (6%) notches were noted in the FVW.

Pregnancies with raised MSAFP

Of the 98 pregnancies examined at 18–22 weeks gestation, 14 (14%) resulted in perinatal death, while of the remaining 84 livebirths, 21 (25%)

Table 1. Reported experience of association between unexplained MSAFP elevation and perinatal complications

Author (year)	*n*	Entry criteria†	MSAFP level	Low birthweight* (%)	Preterm birth** (%)	PNM (%)
Gordon *et al.* (1978)	80	U	>95th	6·3	7·5	3·8
Hamilton *et al.* (1985)	86	U	>2·5 MoM Repeat normal	20·9	20·9	3·5
Hamilton *et al.* (1985)	100	U	>2·5 MoM ×2	25·0	26·0	8 0
Wald *et al* (1977)	94	U	>3·0 MoM	22·0	24·0	4·3
Legge *et al.* (1985)	30	U	>2·0 MoM	33·3	26·7	16·7
Mwambingu (1985)	31	U	>2·5 MoM or >97th×2	25·8	32·2	9·7
Mwambingu (1985)	98	U	>2·5 MoM or >97th×1	8·2	11·2	1·0
Present study	98	R	>2·5 MoM	20·2	25·0	14·3

MSAFP, Maternal serum alpha-fetoprotein.
PNM, Perinatal mortality.
*Defined as <10th centile birthweight or ≤2·5 kg in the study by Wald *et al.* (1977).
**Defined as gestational age at delivery <37 weeks or <36 weeks in the study by Gordon *et al.* (1978).
†U, Unselected, R, referred

were born at ≤37 weeks gestation and 17 (20%) were ≤10th centile in birthweight. These results are compared with previous studies in Table 1.

The RI values were >97·5th centile of our reference range in only 3 of the 27 (11%) pregnancies with poor perinatal outcome (perinatal death or livebirth ≤32 weeks or birthweight ≤5th centile).

At the 18–22 week scan, oligohydramnios was noted in seven pregnancies and in five of these the fetal head and abdominal circumferences were <2·5th centile of our reference ranges. All seven pregnancies resulted in perinatal deaths. An additional three women with normal amniotic fluid volumes had fetal head and abdominal circumferences <2·5th centile; however, these pregnancies were redated and all had normal outcomes. Doppler studies demonstrated a notch in the FVW from either the left or right uterine artery in 18 pregnancies of which seven resulted in intrauterine or neonatal death; three of these were associated with oligohydramnios. Therefore, the presence of a uterine artery FVW notch or oligohydramnios correctly predicted 11 of the 14 (79%) perinatal deaths.

In 11 of the 18 pregnancies with a FVW notch the pregnancies resulted in livebirths (Table 2); however, six of these infants were very preterm (<32 weeks) and/or growth retarded (<5th centile birthweight). Thus, of the 18 pregnancies with a uterine artery notch, 13 (72%) were associated with perinatal complications. Conversely, 66 of the 80 pregnancies with absent notches resulted in livebirths, at >32 weeks gestation with birthweights >5th centile (negative predictive value 82·5%; Table 2).

The relation between the presence of a uterine artery notch and perinatal outcome for the 53 patients assessed again at 24–26 weeks is shown in Table 2. None of the pregnancies with a normal uterine artery FVW at 18–22 weeks went on to develop an abnormal waveform. Of the 18 pregnancies with a notch at 18–22 weeks, 10 were studied a second time and two of them had a normal uterine artery FVW and a normal perinatal outcome. Of the eight pregnancies with a notch on repeat examination, three resulted in perinatal deaths and four resulted in growth retarded (<5 centile birthweight) and/or very preterm (<32 weeks) livebirths. Thus, Doppler assessment at 24–26 weeks gestation improved both the predictive values of a uterine artery FVW notch. The presence of a notch correctly predicted perinatal complications in 7 of 8

Table 2. Perinatal outcome in women with a raised maternal serum AFP who were examined for the presence of a notch on the uterine artery flow velocity waveform (FVW)

	Perinatal outcome*						Predictive value (%)	
FVW	Complications	Normal	Total	P^{**}	Sensitivity (%)	Specificity (%)	Positive	Negative
At 18–22 weeks								
Notch present	13	5	18					
Notch absent	14	66	80					
Total	27	71	98	<0·001	48	93	72	82·5
At 24–26 weeks								
Notch present	7	1	8					
Notch absent	7	38	45					
Total	14	39	53	NS	50	93	87·5	84

*Complicated perinatal outcome includes all perinatal deaths and livebirths ≤32 weeks gestation and/or ≤5th centile birthweight Normal outcome is defined as livebirth >32 weeks gestation and birthweight >5th centile.
**Fisher's exact test.

pregnancies (87·5%), while the absence of a notch was associated wtih good perinatal outcome in 38 of 45 pregnancies (84%; Table 2).

Discussion

In singleton pregnancies an elevated MSAFP in the absence of fetal malformations is associated with an increased occurrence of perinatal mortality, severe IUGR and preterm delivery. Furthermore, the combination of elevated MSAFP, oligohydramnios and abnormal uterine artery Doppler findings selects a subgroup of pregnancies associated with a very poor perinatal outcome.

The data of this study suggest that the presence of a notch in the FVW from the uterine artery is a better predictor of poor perinatal outcome than the RI. Furthermore, although a notch was present in some normal pregnancies at 18–22 weeks gestation, in those patients with a raised MSAFP this characteristic of the FVW, even at this early gestation, will effectively select a subset of patients prone to perinatal mortality, severe IUGR and preterm delivery (<32 weeks). Repeating the Doppler studies at 24–26 weeks gestation improved both the predictive values as well as defining a 'high-risk' group at a gestation when further clinical investigations or management may be affected. In some pregnancies with a normal outcome, the abnormality in the uterine artery FVW at 18–22 weeks disappears by 24–26 weeks presumably because of delayed but normal trophoblastic invasion and placental maturation.

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A pilot study of chemo-radiotherapy in advanced carcinoma of the vulva

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Summary. Advanced squamous cell carcinoma of the vulva (FIGO stages III and IV) has a poor cure rate even with exenterative surgery. We report a pilot study of combined pre-operative chemo-radiotherapy (CHT/RT) in all patients with advanced vulval carcinoma presenting to St Bartholomew's Hospital between July 1987 and March 1989. Twelve patients have been treated, of whom nine had primary lesions (four FIGO stage III and five stage IV) and three had recurrent disease after simple or radical vulvectomy. Seven patients were treated with an initial split course of CHT/RT: there was one treatment-related death and the others have all died following recurrence with a median disease-free survival of 5 months (range 3–12) and a median survival of 7 months (range 3–16). Five patients have received a continuous course of CHT/RT: one died before operation with pulmonary metastases, three patients are disease free at 6 to 9 months, and another patient has been treated with only palliative intent. Toxicity was acceptable in the continuous regimen and this treatment seems to have a promising role in the management of advanced carcinoma of the vulva. A review of the literature on combined therapy is presented.

Squamous carcinoma of the vulva is an uncommon tumour, accounting for approximately 4% of all gynaecological malignancies. There are about 800 cases registered in the UK each year. Although surgery is effective in early disease, with a 5-year survival of 80–90%, some patients present with advanced disease. For these patients surgery often requires some form of pelvic exenteration with an associated high morbidity. Several authors have reported the use of pre-operative radiotherapy to reduce the bulk of the tumour and to allow conservation of bladder and rectal function (Boronow 1982; Hacker *et al.* 1984; Jafai & Magalotti 1981).

Nigro *et al.* (1974) reported the use of combined chemotherapy and radiotherapy (CHT/RT) in patients with squamous cell carcinoma of the anus before conservative surgery and since 1984 this approach has been used as definitive treatment for the disease, with surgery reserved for treatment failures or relapse (Cummings *et al.* 1984). These regimens have used mitomycin-C and 5-fluorouracil (5-FU) given concomitantly with pelvic radiotherapy in various schedules. Evans *et al* (1988) have reported the

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use of low dose pre-operative CHT/RT in three patients with advanced vulval carcinoma, and Kalra *et al.* (1981) have reported one such case. Levin *et al.* (1986) have used a split course regimen similar to that used by Cummings *et al.* (1984) for anal cancer.

Following these early encouraging results we have undertaken a pilot study of combined CHT/RT as a phase 1 trial, and we report preliminary results.

Patients and methods

All patients with advanced squamous carcinoma of the vulva, either primary or recurrent, presenting to the Gynaecological Oncology Department at Saint Bartholomew's Hospital from July 1987 to March 1989 were considered for treatment. Some patients went on to have radical vulvectomy. Those patients with large tumours that might require exenterative surgery were treated with CHT/RT in an attempt to salvage one or other sphincter and avoid the need for either a urinary or faecal diversion.

Twelve patients, with a median age of 73 years (range 53–93), have so far been treated. All patients had an examination under anaesthesia, biopsy, chest X-ray, measurement of plasma urea and electrolytes, liver function tests and a full blood profile; seven had pelvic CT scans. Nine had primary lesions (four FIGO stage III and five stage IV) and three had recurrent disease. Their presenting features, including primary tumour size and extent, stage and histology are shown in Table 1. Three other patients have been seen. Two of these are still undergoing treatment; both had pulmonary metastases at presentation and are being treated with palliative intent.

Treatment

Treatment schedules were largely individualized and details are shown in Table 2. Initially patients received a split course of CHT/RT comprising megavoltage radiotherapy to the pelvis to 25 Gy mid-plane dose (MPD) in 10 fractions in 2 weeks from an anterior-posterior, parallel opposed pair (see Fig. 1). The patients were treated supine and the volume included the true pelvis, vulva and inguinal lymph nodes. The simulated anterior field is shown in Fig. 2. Average

Table 1. Characteristics at presentation

				Primary		FIGO classification		
Patient	PS	Age (years)	MC	Size (cm)/extent	LN size (cm)	Stage	TNN	Histology
1	1	73	COAD	7×4/ into rectum	3×4, bilat. fixed	IV	T4N3	Mod diff
2	0	65	—	8×5/ urethra, upper vag.	4, fixed	IV	T4N3	Well diff.
3	1	73	—	6×6/anus, lower vag	Obturator	IV	T3N3	Well diff
4	4	83	Frail, myxoedema	5×3/ both labia, fixed bone	—	IV	T4N0	Well diff.
5	3	68	Obese, DM	8×5/lower vag.	2, bilat.	III	T3N2	Mod. diff.
6	0	53	—	5×5/ lower vag.	4, fixed	IV (r)	rT3N3	Mod. diff.
7	3	93	Lich. scler	4×4/ urethra	4	III (r)	rT3N2	Mod. diff.
8	3	72	COAD, steroids, A.fib.	20×14/ urethra	4, fixed	III	T3N3	Mod. diff.
9	2	87	CCF	15×10	3, ipsilat.	III	T3N1	Mod diff.
10	1	76	—	6×3/ vag., anus	2, bilat.	III	T3N2	Well diff., verrucous
11	0	74		8×8/vag., rect.	2	IV	T4N1	Mod diff.
12	1	75	—	4×4/urethra	—	III (r)	rT3N0	Well diff.

PS, Performance status (WHO); MC, medical complications; LN, lymph node; COAD, chronic obstructive airways disease; DM, diabetes mellitus; Lich. scler., lichen sclerosis; A. fib., atrial fibrillation; CCF, congestive cardiac failure; vag. vagina; mod. diff., moderately well differentiated.

Table 2. Treatment regimens

	Course 1			Course 2		
	Radiotherapy	Chemotherapy		Radiotherapy	Chemotherapy	
Patient	Gy/#/days	M-C mg/day	5-FU g/day	Gy/#/days	M-C mg/day	5-FU g/day
1	25/10/14	13·5/1	1·35/1–4	20/10/12	10/1	0·5 /1–5
2	25/9/12	19/1	1·6/1–5	Not repeated		
3	22·5/9/12	17/1	1·7/1–5	25/10/14	10/1	1/1–4
4	25/10/20	7/1	0·5/1–4	25/10/12	10/1	0·5/1–4
5	25/10/14	12/1	1/1–4	25/10/13	10/1	1·6/1–3
6	22·5/9/11	17/1	1·28/1–5	25/10/13	17/1	1·28/1–5
7	25/10/11	0	0·5/1–5	Not repeated		
8	45/20/28	12/1	1·25/1–4 28–31	Not applicable		
9	45/25/35	14/1	1·4/1–4	Not applicable		
10	45/20/28	15/1	1·5/1–4 28–31	Not applicable		
11	45/25/35	14/1	1·4/1–4 28–31	Not applicable		
12	45/20/28	12/1	1/1–5 21–25	Not applicable		

#, Fraction; M-C, mitomycin-C; 5-FU, 5-fluorouracil.

field sizes were 22×27 cm. After an interval of 1 month this treatment was repeated. On day 1 of each course patients received a bolus of mitomycin-C, 10–12 mg/m^2, and a continuous infusion of 5-FU at 750–1000 mg/m^2/24 h was given and continued for 4–5 days.

Due to local toxicity this regimen has been changed to comprise a continuous course of radiotherapy in which similar parallel opposed fields are used to deliver 45 Gy MPD in 20–25 fractions in 28–35 days. A bolus of mitomycin-C, 10 mg/m^2 (maximum 15 mg), is given on day 1, and an infusion of 5-FU, 750 mg/m^2 (maximum 1·5 g/24 h), is given on days 1 to 4; 5-FU infusion is repeated in the last week of radiotherapy (see Fig. 1). Doses were modified in patients aged over 80 years and the second course was modified when leuco- or thrombocytopenia occurred.

Response was as defined by the International Union Against Cancer (UICC), i.e. a complete

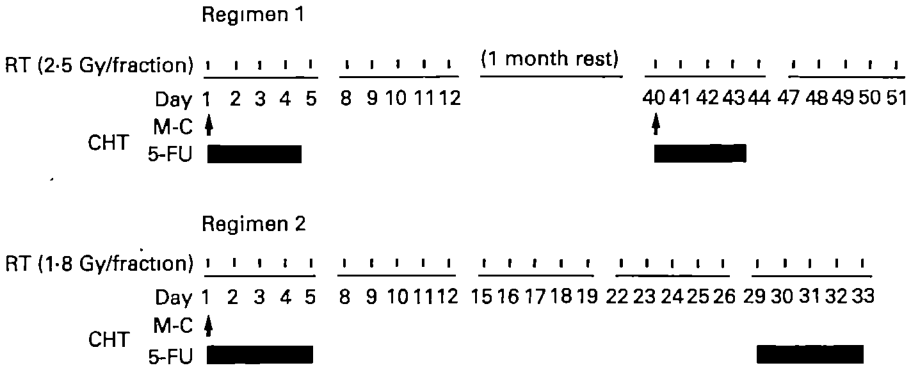
Regimen 1
RT (2·5 Gy/fraction)
(1 month rest)
Day 1 2 3 4 5 8 9 10 11 12 40 41 42 43 44 47 48 49 50 51
CHT
M-C
5-FU
Regimen 2
RT (1·8 Gy/fraction)
Day 1 2 3 4 5 8 9 10 11 12 15 16 17 18 19 22 23 24 25 26 29 30 31 32 33
CHT
M-C
5-FU

Fig. 1. Combined chemotherapy (CHT) and radiotherapy (RT). Treatment regimens: MC, mitomycin-C; 5-FU, 5-fluorouracil.

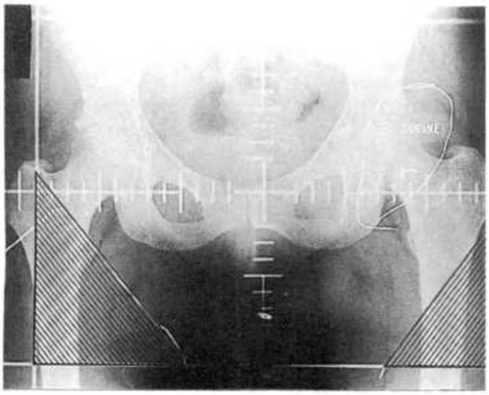

Fig. 2. Film of a simulated anterior field. Wire outlines a large, left inguinal lymph node mass. An introital marker can be seen and lead shielding for the thighs is also indicated.

response is resolution of all detectable diseases and a partial response is a reduction in measurable disease of at least 50%. Responses have to be maintained for at least 3 months. All patients have been followed until death or for a minimum of 16 months.

Results

Table 3 shows the outcome of CHT/RT and surgery. Five patients have had surgery, one awaits surgery and three died before operation (one death related to treatment and two with pulmonary metastases). Two patients were considered unfit for surgery and so received CHT/RT with only palliative intent. One other patient has had a complete response confirmed by examination under anaesthesia and will only undergo radical vulvectomy if recurrence occurs.

Five patients completed the full split course regimen with two complete responses and three partial responses. Two patients (nos 3 and 6) in the latter group went on to have a radical vulvectomy with complete excision of persistent disease and one patient (no. 1) died of septicaemia within days of completing the second course of CHT/RT and so had no surgery. Of the two patients who demonstrated a complete response to split CHT/RT, one (no. 4) was never fit for surgery, and had been treated with palliative intent; the other (no. 5) did not undergo surgery because she developed pulmonary metastases. Two other patients planned for split course CHT/RT received only the first half of treatment. One of them (no. 2) developed severe enteritis (WHO grade 3) and, after total parenteral nutrition for 1 month, underwent radical vulvectomy which identified residual disease. Local recurrence occurred and she died 4 months later. The other patient (no. 7), aged 93, underwent a local excision following marked tumour regression. The tumour recurred at 12 months and was treated with an ^{192}Ir wire implant, leading to partial response lasting 16 months. She died shortly after further recurrence. Patients treated by the split course regimen had a median disease-free survival of 5 months (range 3–12 months) and an overall median survival of 7 months (range 3–9 months).

Of five patients treated with continuous CHT/RT, one (no. 8) developed pulmonary metastases after 3 months and therefore did not undergo surgery. She died after 4 months with the local disease controlled. One patient (no. 9) received the continuous course with palliative intent and died at 6 months. Of the two patients who have had a radical vulvectomy, one (no. 10) had residual tumour in the vulva and she remains disease free at 9 months, while in the other (no. 12) no residual tumour was identified. One patient (no. 11), who had an 8-cm stage IV tumour, is in complete remission after CHT/RT, and radical vulvectomy is being reserved for treatment of local recurrence, if it occurs.

Toxicity

In general the more severe grades of toxicity were experienced by patients receiving the split course CHT/RT, while those receiving the continuous course had only mild to moderate toxicity.

Skin. The local morbidity was as expected. All patients developed perineal skin reactions, (moist desquamation in 14 of 17 courses of treatment), beginning after 10–12 days and with a mean duration of 5 days following each course.

Bowel. In 12 split courses of treatment most patients were affected by mild diarrhoea (grade 1–2), more often during the second course, and one patient developed grade 3 colitis. Diarrhoea has been much less for patients treated by the continuous regime.

Bone marrow. One patient developed marked myelosuppression with a neutrophil count of $0{\cdot}84\times10^9$/l and a platelet count of 96×10^9/l. She

Table 3. Response to chemo-radiotherapy and outcome after surgery

Patient	Response	Surgery	Disease-free interval (months)	Outcome
1	PR	Nil	No DFS	Dead at 3 months, septicaemia
2	PR	Radical vulvectomy	8	Dead at 9 months, local disease
3	PR	Radical vulvectomy	6	Dead at 8 months, local disease
4	CR	Nil (palliative)	5	Dead at 7 months, pelvic disease
5	CR	Nil (lung mets)	3	Dead at 3 months, local control
6	PR	Radical vulvectomy	5	Dead at 9 months, local disease
7	PR	Local excision	12	Dead at 16 months
8	CR	Nil (lung mets)	3	Dead at 4 months, local control
9	PR	Nil (palliative)	No DFS	Dead at 6 months, local disease
10	PR	Radical vulvectomy	No recur	NED at 9 months
11	CR	Not planned, EUA and biopsy NED	No recur	NED at 7 months
12	CR	Radical vulvectomy	No recur	NED at 6 months, no residual tumour at vulvectomy

DFS, Disease-free survival; EUA, examination under anaesthesia; NED, no evidence of disease; PR, partial response; CR, complete response; mets, metastasis.

had been a chronic bronchitic, had poor respiratory function and died from respiratory failure, septicaemia and pneumonia. A further patient developed a neutrophil count of $0{\cdot}9\times10^9$/l with no sequelae. One patient developed a marked oral mucositis following 5-FU infusion.

One patient had delayed wound healing after radical vulvectomy but local recurrence was eventually identified. Another patient developed perineal cellulitis 1 month after CHT/RT.

Discussion

The results of treatment of stage I and II carcinoma of the vulva are good with 80–90% of patients cured by surgery alone (Rutledge *et al.* 1970). However, the prognosis for patients with stages III and IV disease is poor with any treatment. From a total of 1100 patients the 5-year survival of those with stage III disease was only 28% and stage IV less than 5% (FIGO 1985). With small lesions a radical vulvectomy will control most tumours and conserve bladder and bowel function. More advanced lesions require increasing degrees of exenterative surgery with predictably high morbidity and mortality in this largely elderly group. Even in experienced hands radical vulvectomy with pelvic exenteration in selected cases gives a 5-year survival of only 47%, and patients with clinically involved nodes are not long-term survivors (Cavanagh & Shepherd 1982). Combined modality treatment has therefore been explored with the aim of permitting more conservative surgery to be performed. Several different radiation schedules have been utilized for this purpose.

Frischbier & Thomsen (1971) reported a series of 118 patients (including 85 with stages III and IV) treated with high energy electron therapy to the vulva and groins. They found a 5-year survival of 39% in patients with advanced disease. Hacker *et al.* (1984) reported the use of radiotherapy and surgery in eight patients (two with T4 and six with T3). Doses of megavoltage radiation of 44–54 Gy by external beam were, in general, well tolerated and were followed by radical vulvectomy or wide local excision. Five had no evidence of disease at 2–10 years, and the other three had disease controlled for 15–22 months. Surgical specimens often showed residual microscopic disease, despite a clinical complete response after radiotherapy.

Acknowledging the difficulty of deciding individual tumour cell viability in these circumstances, the authors recommend the combined approach. However, a high late complication rate was seen, with 24% of patients developing ulcers and 5% extensive tissue necroses. This may have been due to the large fraction size of 3 Gy used. The 33 patients described by Boronow (1982) (mostly stage III) were treated with external beam or radium (46%) or both (54%) and had a 5-year disease-free survival rate of 65%. Their average age was under 70 years. Except for two patients who had N3 disease and were controlled, node status was not recorded. High doses of radiation were used and again a high complication rate was seen with one treatment-related death, four fistulas, five necroses (three introital, one pubis & one hip), three urethral strictures requiring surgery and one lymphoedema. Patients with recurrent disease in this series had a similar 5-year survival (71%). Lastly, Backstrom *et al.* (1972) reported a 5-year survival of 21% in patients with T4 disease. Radiation therefore seems to have a role in advanced vulval cancer.

As in combined treatment for anal cancer, the addition of chemotherapy allows the use of lower doses of radiotherapy and may have a synergistic effect (Nigro *et al.* 1974). Iverson (1982) first used chemotherapy (bleomycin), and radiotherapy for inoperable cases with some success. More recent reports have indicated 50–66% long-term control with CHT/RT (Evans *et al.* 1988; Levin *et al.* 1986). The results in our patients are less favourable so far, our longest survival period being 16 months. Eight patients have died within 3 to 9 months of presentation, with recurrence of disease developing within 3 to 8 months.

There are several reasons for this adverse outcome. Firstly, our patients had very advanced disease: 50% had stage IV (including three with fixed nodes) and one with stage III had fixed nodes. Secondly, three had recurrent disease. Thirdly, the patients were older than in other series, with a median age of 73 years and, in general, they were less fit, with four patients having WHO performance status of 3 (spending more than 50% of the day in bed). Also there was no selection for treatment.

The toxicity of the first split course CHT/RT regimen was marked, with one treatment-related death from sepsis and one severe radiation enteritis requiring parenteral nutrition. Most skin reactions comprised mildly debilitating moist desquamation, and no skin necrosis was seen. The toxicity was due to the high doses of mitomycin-C and 5-FU, which were not initially adjusted for age. Also, higher doses per fraction of radiation were used in the split course regimen which may have added to the briskness of the reaction. Toxicity (in particular diarrhoea) has been reduced in the continuous course regimen. One patient had a severe oral mucositis due to 5-FU and now all patients receive allopurinol mouthwashes, which have been shown to reduce this side-effect (Clark & Slevin 1985).

It is concluded that advanced carcinoma of the vulva has responded to combined chemo-radiotherapy. The continuous course of CHT/RT has been well tolerated in this study and has permitted the use of conservative surgery in an attempt at cure. It has also been used alone as 'palliative' treatment in patients unsuitable for major surgery.

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Thrombotic thrombocytopenic purpura in pregnancy with maternal and fetal survival. Case report

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Case report

A 25-year-old woman was admitted to hospital at 28 weeks gestation because of gingival bleeding for one day with a low platelet count. The pregnancy had been uneventful before that. She had had a normal pregnancy four years previously and had used oral contraceptives in the last three years. On examination, the patient was a thin young woman with diffuse ecchimoses and petechiae, especially on the legs. The liver and the spleen were not enlarged. Neurological examination was normal. Blood pressure was 130/80 mmHg and the temperature 38·5°C. Uterine size was consistent with the stated gestation and the fetal heart tones were audible. Haemoglobin was 9·4 g/dl, platelet count 29×10^9/l, white blood cell count 12×10^9/l, reticulocytes 0·075%. A peripheral blood smear showed many schistocytes and fragmented red cells. Further testing revealed normal urea nitrogen and serum creatinine. Clotting studies showed a decrease of fibrinogen (1·70 g/l) and a normal level of serum fibrin degradation products. Urinalysis showed microscopical haematuria and a 1+ reaction for protein. Bilirubin was 30·8 μmol/l, lactic dehydrogenase 1225 units/l (normal values up to 450 units/l); haptoglobin was undetectable. Within a few hours after admission she had nose bleeding and complained of headache and paraesthesia of the left limbs. On the following day she complained of increasing headache, chest pain, paraesthesia, tremor, lumbar and lower limb pain. A diagnosis of thrombotic thrombocytopenic purpura was made and fresh frozen plasma was infused. The haemoglobin fell to 7·4 g/dl and platelet count reached 7×10^9/l. Direct Coombs' test and antiplatelet antibodies were negative. A computed tomographic scan of the brain was normal. Fresh frozen plasma (4 units daily) was infused as well as prednisolone, 1 g/day, acetylsalicylic acid, 500 mg twice daily, and dipyridamole, 75 mg every 6 h. On the fourth hospital day plasma exchange therapy was begun. Seven daily procedures were performed with a continuous flow cell separator (Celltrifuge II, Fenwal). In each procedure approximately 40 ml/kg of plasma were substituted with fresh frozen plasma collected by donor plasmapheresis. In the first treatment the volume exchanged was about 20 ml/kg because of symptoms of hypocalcaemia (citrate induced). Anticoagulation was obtained with acid citrate dextrose (ACD formula A) in the first treatment and then with continuous infusion heparin. On the third day of therapy the platelet count and the haemoglobin began to rise together with a clinical improvement (Fig. 1). At the 10th day from admission the platelet count was 171×10^9/l and plasma exchange was withheld. By the 18th hospital day she was discharged, after an ultrasound examination showed a normally progressing pregnancy. Treatment at discharge was acetylsalicylic acid, 200 mg every other day, dipyridamole, 75 mg

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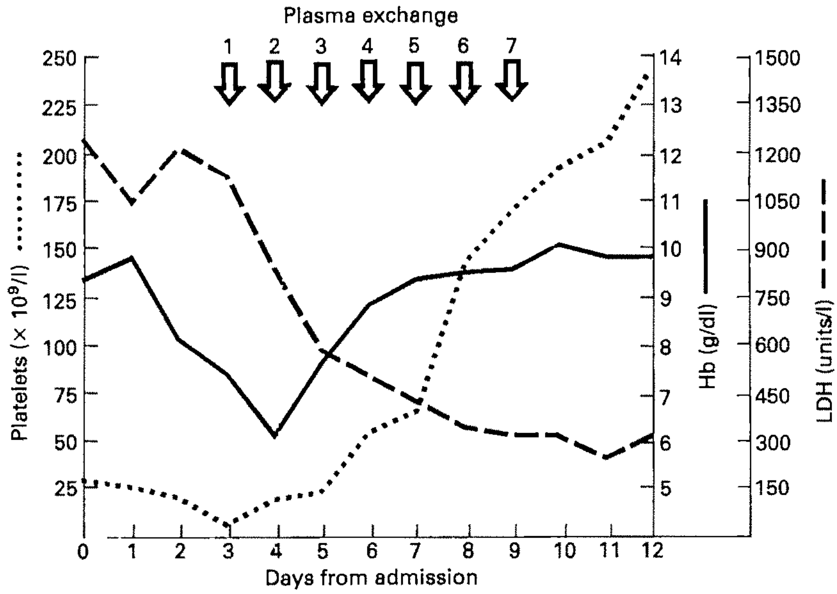

Fig. 1. Platelet count, haemoglobin and lactic dehydrogenase values along with plasma exchange procedures.

every 6 h, prednisone to be tapered, ranitidine and folic acid. Blood cell count remained normal over the subsequent weeks. At 35 weeks gestation she was admitted to hospital because of premature prelabour rupture of the membranes and a day later she had a spontaneous vaginal delivery of a healthy 2700 g female infant with Apgar scores of 9 and 10 at 1 and 5 min respectively. Maternal Hb was 10·3 g/dl; the platelet count was 245 × 10^9/l. Prednisone was stopped and she was discharged with dipyridamole, 75 mg every 8 h, and acetylsalicylic acid, 200 mg every other day. Five months later, all medication was stopped. She maintained a normal blood count level and is now (18 months later) in good health.

Discussion

Thrombotic thrombocytopenic purpura (TTP) is a rare severe disease characterized by thrombocytopenia, microangiopathic haemolytic anaemia, neurological abnormalities and often fever and renal failure, possibly caused by the lack of a serum inhibitor of platelet aggregation (Marcus 1982; Aster 1985). The main problem is to establish a correct diagnosis: the condition can be confused with pre-eclampsia, disseminated intravascular coagulation, Werlhof purpura or Evans' syndrome. Pre-eclampsia was excluded by normal blood pressure and minimal proteinuria, disseminated intravascular coagulation by normal clotting indices and absence of fibrinogen split products or fibrin monomers; Werlhof and Evans' syndromes are associated with an immunologically mediated platelet (and erythrocyte) destruction with no neurological complaints. This patient had the main features of TTP, except renal failure. The relation between pregnancy and TTP is obscure. There are a few reported cases where delivery was beneficial in pregnant women with TPP, thereby supporting a causative or permissive role of pregnancy (Natelson & White 1985). Other authors have suggested that the occurrence of TTP in pregnancy is merely coincidental. A large multicentric Italian study involving 29 patients did not report any case in pregnancy (Ascari *et al.* 1986). The rarity of the disease precludes large studies on TTP in pregnancy. The prognosis of TTP in pregnancy in the past has been very poor both for mother and fetus (Schwarz & Brenner 1978; May *et al.* 1976; Davis 1984). The fetus is not apparently involved in the process but may suffer from maternal organ damage or placental insufficiency. Recently cases have been reported showing a good outcome of the pregnancy after plasma exchange and/or plasma infusion (Ambrose *et al.* 1985; Vandekerckhove *et al.*

1984). Plasma exchange therapy seems to have changed the prognosis of TTP (Aster 1985; Kwaan 1985). In our patient, who was apparently not responding to infusion of plasma alone, the therapy with plasma exchange did cause a reversal of symptoms, rapid improvement of laboratory variables and a normal outcome of the pregnancy. We suggest that early and intensive plasma exchange treatment should be undertaken to enhance maternal and fetal survival. Gestational age may prove to be an important factor in fetal prognosis as well as in the susceptibility to maternal damage and to enable early delivery. On the other hand delivery does not seem to be crucial for the prognosis in the mother. Nevertheless pregnancy should be discouraged in patients who experienced TTP since platelet aggregation can be enhanced in a woman who has a pre-existing biochemical defect.

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Abnormal ovarian cell line: a cause for ovarian failure. Case report

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Case report

A 32-year-old Lebanese woman attended our endocrinology clinic having had primary infertility for 14 years and secondary amenorrhoea for 7 years. Her menarche occurred at the age of 13 years and was followed by 12 years of oligomenorrhoea. She had had no relevant systemic disease or deep X-ray exposure. She had a feminine appearance, she was 153 cm tall and weighed 64 kg. She had a negative response to a 5-day course of medroxyprogesterone acetate (10 mg/day). She had normal thyroid function and serum prolactin. Her serum follicle-stimulating hormone (FSH) exceeded 50 iu/l on three occasions. No antibodies were detected for adrenal, thyroid, ovarian or gastric tissues. Lymphocytic karyotyping, using the trypsin Giemsa banding technique, showed a normal 46 XX karyotype; 100 cells were screened. Laparotomy was performed. The uterus and both tubes were of normal shape but small in size. The left ovary was cord like. The right ovary was small, of normal shape and texture in the centre, but tapering towards both ends. Both gonads were biopsied for histopathological examination and tissue culture.

Histopathological examination of both gonads showed normal ovarian stroma. In the right ovary there were some inclusion cysts from the surface epithelium and corpora albicantia and structures reminiscent of atretic follicles. Examination of multiple sections did not reveal any primary follicles or germinal epithelium (Fig. 1).

Tissue cultures of ovarian biopsies were set up as described by Hayflick & Moorhead (1961) and chromosomal analysis was done as described by Moorhead *et al.* (1960). One hundred cells were examined. They all showed a karyotype of 45, XO t(3;20) (q22;q12) t(13;15) (q14;q13) (Fig. 2). The family pedigree showed no similar condition.

Discussion

Secondary amenorrhoea due to ovarian failure is a fairly common diagnosis. This patient showed a rare combination of a unilateral streak gonad and a hypoplastic ovary with normal peripheral karyotyping and aberrant ovarian cell line. The presence of two X chromosomes was obviously not necessary for the development of the right ovary despite the complex chromosomal rearrangement involving chromosomes number 3, 20, 13 and 15. This is to our knowledge the first report of this abnormal ovarian chromosomal combination. It also shows that a woman with an abnormal ovarian karyotype may not have any unusual somatic features and may have irregular ovarian activity for a long time. This occurred for 12 years in our patient. A normal lymphocyte karyotype may not reflect the chromosomal status of the ovaries or exclude an aberrant cell line in other tissues (Kemmann *et al.* 1982). Routine ovarian tissue karyotyping can provide useful additional information in women with primary ovarian failure with a normal lymphocyte karyotype and may detect an unexpected Y chromosome with its potential for inducing gonadal malignancy.

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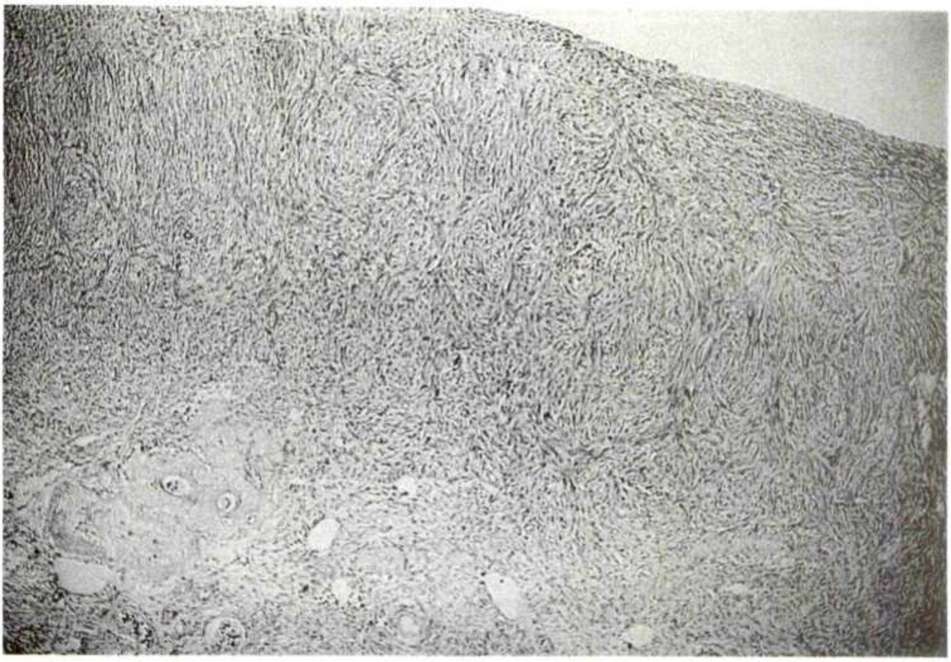

Fig. 1. Haematoxylin and eosin stained section of the right ovary. The corpus albicans indicates previous ovulation. ×35.

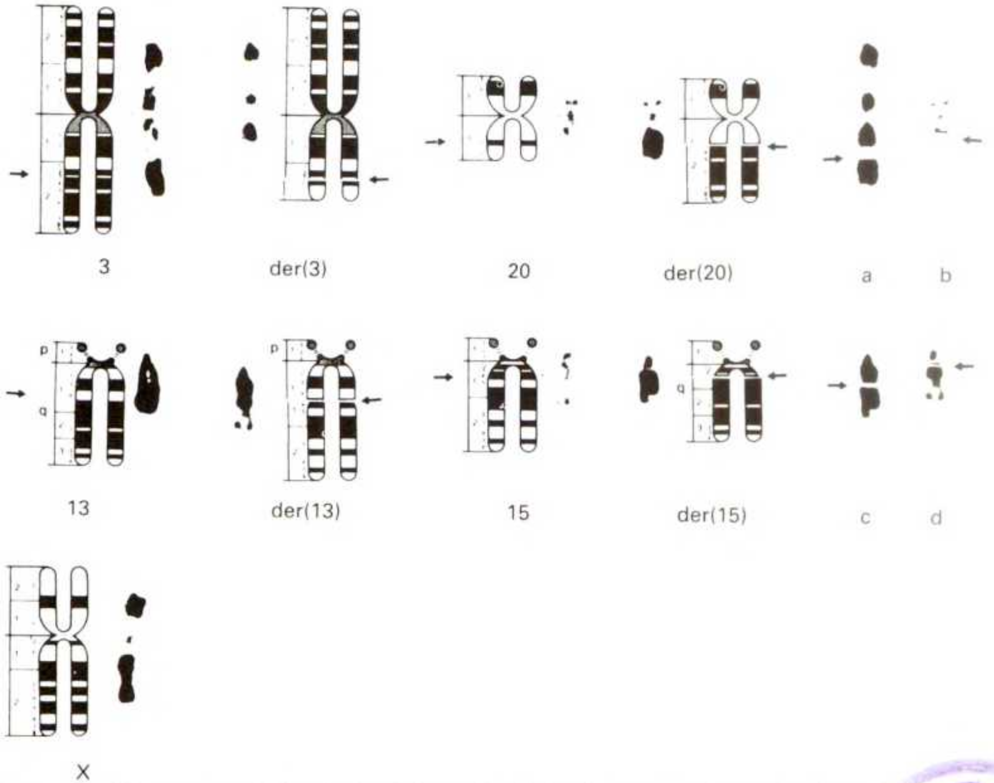

Fig. 2. Partial karyotype (G-banding) of the proband showing reciprocal translocation: 45, XO t(3;20) (q22;q12) t(13;15)(q14;q13). Theoretical rearrangement of the abnormal or derived (der) chromosomes is shown by a, b, c and d. Break points are indicated by arrows.

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Fetal vesicorectal fistula causing oligohydramnios in the second trimester. Case report

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Case report

A 26-year-old woman in her first pregnancy had a normal serum α-fetoprotein level at 16 weeks. A routine ultrasound scan at 21 weeks showed severe oligohydramnios with fetal dimensions on the 5th centile.

Transvaginal ultrasound showed that the fetal bladder and kidneys were normal. Increased echogenicity was seen in the fetal abdomen raising the possibility of meconium peritonitis.

In order to obtain a better ultrasonic view of the fetal anatomy and to exclude concealed premature rupture of membranes, written consent was obtained from the woman to perform amnioinfusion with warm normal saline at a rate of 20 ml/min. Intra-amniotic pressure rose from 1 to 5 mmHg after 300 ml had been infused and did not exceed the normal range for gestation (Nicolini *et al.*, 1989a). The stomach, which was not seen previously, then filled. It then became apparent that the increased abdominal echogenicity was due to a sausage-shaped cystic structure 3·5 × 1·5 × 1·5 cm anterior and lateral to the left kidney extending downwards behind the bladder. This had highly echogenic contents within an anechoic rim and was thought to be an encapsulated collection consequent to bowel perforation. No other abnormalities were seen. Umbilical artery flow velocity waveforms were normal. Fetal breathing and body movements were observed minutes after amnioinfusion. Fetal blood sampling showed that the pH and gases were normal and that the karyotype was 46XY.

At 24 weeks gestation the severe oligohydramnios persisted despite the bladder filling and emptying and the fetal intra-abdominal structures remained indistinct. In order to clarify the diagnosis, fetal intraperitoneal infusion was performed (Nicolini *et al.*, 1989b).

Peritoneal fluid aspirated after instillation of 30 ml of warm saline showed no meconium. The transverse colon, sigmoid colon and rectum were noted to be dilated. Peristalsis and antiperistalsis were oberved in the transverse but not in the sigmoid colon. Anal atresia with vesicorectal communication was suspected. The association of lung hypoplasia with oligohydramnios (Nicolini *et al.*, 1989c) and the possible but unestablished benefit of repeated amnioinfusions in reducing the chances of this complication was explained to the patient. The risks of possible intrauterine infection with or without preterm labour with such management were also discussed. Amnioinfusion of 300–600 ml of saline was performed weekly from 25 to 30 weeks gestation. Infusion was at a rate of 20 ml/min and the amniotic pressure was measured during infusion to maintain normal pressures for that gestation. Amniotic fluid volume was observed to be slightly reduced by the third day, but minimal amniotic fluid was found on each occasion before the infusion. Fetal breathing movements were stimulated by each amnioinfusion. The fetal chest/abdominal circumference ratio, the length of femur and the head circumference plotted against gestation were along the 5th centile. Fetal growth and umbilical artery blood flow patterns remained normal.

At 29 weeks the amniotic fluid lecithin/sphin-

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gomyelin ratio was two. At 30 weeks, two days after the last amnioinfusion, the patient was admitted with painful contractions and blood-stained discharge. She had no pyrexia and there was no tenderness over the uterus. There was fetal tachycardia of 200/min with decelerations. A male infant was born by caesarean section. The baby weighed 1485 g with Apgar scores of 6 and 8 at 1 and 5 min, the cord artery blood pH was 7·18. There was difficulty in ventilating the infant from birth suggesting a clinical diagnosis of lung hypoplasia. He died aged 6 h. Post-mortem examination showed anal atresia, vesicorectal fistula, colonic distension, a thin distended bladder, an intact urethra, hypospadia and undescended testes. Squeezing the bladder emptied urine into the rectum with no leak via the urethra. The lung to body weight ratio of 0·015 was on the lower limit of normal for gestation (Wigglesworth *et al.*, 1981). Histological examination showed no infection in the lung or the placenta.

Discussion

The most common causes of severe oligohydramnios in the early second trimester are premature rupture of the membranes, fetal urinary tract obstruction, renal agenesis and severe intrauterine growth retardation.

Whatever the cause, early onset oligohydramnios is associated with poor fetal outcome, especially in the presence of raised serum alphafetoprotein (Seller & Child, 1989; Balfour & Laurence 1980; Koontz *et al.*, 1983; Barss *et al.*, 1984; Dyer *et al.*, 1987).

Techniques which help in the differential diagnosis include infusion of saline into the uterine cavity (amnio-infusion) to improve ultrasound examination (Gembruch & Hansmann 1988), Doppler studies of fetal and uteroplacental circulations to identify severe intrauterine growth retardation and fetal blood sampling to determine acid base status and karyotype (Nicolaides *et al.*, 1986).

In our patient the aetiology of oligohydramnios remained obscure after the above measures, necessitating additional procedures. Peritoneal instillation of saline excluded meconium peritonitis. The demonstration of bladder filling and emptying in the presence of oligohydramnios was puzzling and the possibility of a vesicorectal communication was entertained after observing peristaltic movements within distended bowel loops. The preferential direction of urinary flow from the bladder to the rectum rather than to the amniotic fluid remains to be explained in the presence of normal urethra. The fact that distention of the colon did not increase despite continuous inflow of urine is consistent with the colon's role in water reabsorption.

It has recently been suggested that pulmonary hypoplasia is due to low intra-amniotic pressure secondary to oligohydramnios (Nicolini *et al.*, 1989c) and experimental studies in animals together with anecdotal evidence in humans support a role for amnioinfusion in the prevention of pulmonary hypoplasia (Nicolini *et al.*, 1989a,c). Although serial amnio-infusions are technically feasible (Nicolini *et al.*, 1989c, Gembruch & Hansmann, 1988), two problems remain: the gestational age at which this procedure should be started and the cumulative procedure-related risk. Amnio-infusions carry some risk of chorioamnionitis and an up to 12% risk per procedure of immediate rupture of membranes (Gembruch & Hansmann 1988). Although the patient presented with clinical features suggesting chorioamnionitis after the fifth procedure, our experience with repeated entry into the amniotic cavity for intravascular transfusions in Rh disease suggests that repeated amnion puncture at two to three week intervals may be a safe procedure if careful aseptic technique is used and prophylactic antibiotics are given. Care must be taken not to exceed the intrauterine pressure appropriate for that gestation. Despite five amnioinfusions the membranes remained intact, probably because of our practice of intrauterine pressure monitoring during the procedure and thus the avoidance of excessively high intra-amniotic pressures (Nicolini, *et al.* 1989a).

The failure to prevent clinical lung hypoplasia might be related to relatively late intervention or alternatively, weekly amnioinfusion may not have maintained adequately the intra-amniotic pressure needed for proper lung development. Small chest circumference and absent fetal breathing movements (Songster *et al.*, 1989; Blott *et al.*, 1987) are reported to be predictive of lung hypoplasia. These variables, however, were normal in this patient and the lung/body weight ratio was on the lower limit of normal, even though the infant could not be ventilated. Further experimental work in animals together with better knowledge of the natural history of such cases in humans should provide better guidelines to the appropriate management.

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SHORT COMMUNICATIONS

The rational use of coagulation studies in obstetrics: an audit

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Coagulation failure is undoubtedly one of the most frightening and serious of obstetric complications and in some conditions the use of coagulation studies is vital and life saving (Letsky 1986). Often, however, these tests appear to be performed uncritically on trivial indications. We performed a retrospective audit to see whether they could be safely used in a more selective and rational manner with consequent savings.

Subjects and method

During a 12-month period between 1986 and 1987, 3900 women were delivered at Dudley Road Hospital, Birmingham. All pregnant women who had coagulation studies performed were identified from the computerized haematology records and their case notes studied. Unit policy was to screen any woman who clinically presented with an abruption, moderate to severe pre-eclampsia or prolonged intrauterine death for potential coagulation abnormalities. Investigations performed included partial thromboplastin time (PTT), prothrombin time (PT), and platelet counts on all patients. Levels of fibrinogen and fibrin degradation products (FDP) were requested in selected cases. These results were noted and correlated with the clinical situation.

Results

Overall 328 women had a total of 426 studies performed. Where more than one study had been performed, the most abnormal was recorded. Platelet counts, PTT and PT results were available for all women, but fibrinogen and FDP levels in only 21. The latter have therefore not been included in the analysis.

Normal values for our laboratory were defined as PT < 16 s, PTT < 48 s and platelets $\geqslant 150 \times 10^9$/litre. Abnormal values were defined as PT > 18 s. PTT > 54 s and platelets $< 100 \times 10^9$/litre. Intermediate values were classified as borderline. Results are presented in Table 1.

Discussion

Almost all coagulation studies in pregnancy are carried out to detect disseminated intravascular coagulation (DIC), a complication of pre-eclampsia, abruption, fetal intrauterine death and amniotic fluid embolism. Of the 328 women in our study, only three had significant DIC requiring treatment. One patient with a post-natal septicaemia developed clinical signs of DIC and was found to have deranged coagulation studies. No other women with subsequent DIC were missed before they had clinical signs. This audit confirmed a clinical impression that many coagulation studies were performed with little clinical basis, the unit policy being extended without thought by both obstetricians and anaesthetists to patients who were not in high risk groups. Hypertension (recorded range 125/75–180/120 mm Hg) was the largest group where indications appeared confused. Often these tests are performed at the insistence of the anaesthetist prior to an epidural. There is no evidence that non-proteinuric hypertension is associated with coagulation abnormalities. Despite this, these tests were requested in 76 such women, some in fact being normotensive, but having had slightly raised blood pressure at some stage during the pregnancy. Neither did any of the 77 women with a trace or 1+ of protein have

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Table 1. Audit of coagulation studies in 328 pregnancies

Indication for test	Total no	Platelets			PT			PTT		
		N	B	A	N	B	A	N	B	A
Raised BP	195	176	18	1	190	5	0	182	11	2
APH	66	57	7	2	60	3	3	60	5	1
Pain	14	13	1	0	14	0	0	14	0	0
Fetal death	13	13	0	0	12	1	0	13	0	0
PPH	11	8	0	3	7	3	1	9	0	2
Placenta praevia	4	4	0	0	4	0	0	4	0	0
Pyrexia	3	3	0	0	3	0	0	2	1	0
Miscarriage	4	3	1	0	4	0	0	4	0	0
Septicaemia	2	1	0	1	1	0	1	1	0	1
Abnormality	3	3	0	0	3	0	0	2	1	0
Jaundice	2	2	0	0	2	0	0	1	1	0
Others	11	10	0	1	10	1	0	11	0	0
Totals	328	293	27	8	310	13	5	303	19	6

N = normal range as defined in text, B = borderline range as defined in text, A = abnormal range as defined in text; PTT = partial thromboplastin time, PT = prothrombin time; APH = antepartum haemorrhage; PPH = postpartum haemorrhage; BP = blood pressure

any abnormality. Serial platelet counts are useful in diagnosing and managing pre-eclampsia, a fall always preceding any abnormality in the coagulation pathway (Weenink *et al.* 1985; Redman *et al.* 1978). On occasions pre-eclampsia may develop in an atypical manner with few classical signs (Fusi *et al.* 1989) or as the HELLP syndrome (Sibai *et al.* 1986). A low platelet count will show the need for further investigation including a check on coagulation factors. A reduced platelet count or moderate to severe disease would thus appear clinical indications for checking a PTT and PT

Placental abruption appears the commonest cause of significant DIC. All women with suspected placental abruption were screened, totalling 66 women. Of these 43 were classified as small or slight bleeds, many subsequently proving to be a heavy show. All the abnormal results recorded were in women with a moderate to severe bleed and other clinical signs pointing to the diagnosis. In 14 women abruption was only suspected by abdominal pain, and none had abnormal results. The possibility of a concealed abruption exists, however, and these were probably justified. Prolonged intrauterine death is a well recognised cause of chronic DIC. However, changes tend to be slow and only occur after several weeks. Requesting such tests on the day of fetal death, and again the following day, is unlikely to be of clinical value (Hodgkinson *et al.* 1964; Constantine & Menon 1987).

Of the remaining tests, some were clinically indicated i.e. jaundice and septicaemia (Beller 1985), whilst others would be hard to justify e.g fetal abnormality, decreased fetal movements and known placenta praevia.

Based on the literature and these findings we would suggest a low platelet count, moderate to severe pre-eclampsia, moderate to severe abruptions and prolonged fetal death as being the main indications for requesting a PTT and PT, together with a platelet count. Often the platelet count alone will act as a screening test. Other indications such as septicaemia should be assessed on an individual basis with regard to the clinical situation.

Approximate costs of investigation are: PTT £2.50, PT £2.00, FDPs £3.00, fibrinogen £3.00 and platelets £3.00 (as part of Coulter count), to which can be added the cost of around £10 for an on-call request out of hours. Using these guidelines in our hospital no abnormality would have been missed and a saving of nearly £3000 made.

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Use of Gynocheck endometrial tissue sampler in infertility

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It has been reported previously that the disposable Gynocheck device (Roussell Laboratories Ltd, Uxbridge, Middx) is well tolerated by patients and obtains material adequate for histological investigation (Segedal & Iversen 1983; Iversen & Segedal 1985). These women were predominantly postmenopausal and the prime concern was screening for malignant disease. The present study was designed to determine whether Gynocheck could obtain material suitable for the histological dating of the endometrium, and furthermore whether a young, otherwise healthy, infertile population would find its use acceptable.

Subjects and results

The study included 20 women. Premenstrually, under general anaesthesia and after laparoscopy and dye hydrotubation, a single stroke anterior wall endometrial biopsy was obtained with a sharp uterine curette. The Gynocheck device was then introduced into the uterus and advanced until the tip reached the fundus, the outer sheath was withdrawn, and it was rotated three times clockwise and three times anti-clockwise, while being moved gently up and down. The outer sheath was replaced and the device withdrawn. The specimens were immediately fixed in Bouins solution, bottled separately and labelled randomly either A or B, so that the histologist was blind regarding the instrument used. Specimens were considered adequate if they could be dated histologically using the criteria of Noyes *et al.* (1950).

Of the 20 endometrial biopsies obtained with the Gynocheck device 7 (35%) were considered adequate for histological dating and 13 (65%) inadequate; the corresponding findings for the curette biopsies were 17 (85%) adequate and 3 (15%) inadequate.

Of 13 inadequate Gynocheck biopsies 11 were severely fragmented and in two insufficient material was obtained. A diagnosis of luteal phase defect was made in three biopsies. The three women with inadequate curette biopsies also had inadequate Gynocheck biopsies.

To assess patient acceptability, it was intended to recruit infertile women from the clinic, who would have a Gynocheck biopsy without anaes-

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Discussion

To ensure that an adequate specimen of endometrium was obtained from each patient, the standard curette biopsy was taken first. According to Davidson *et al.* (1987) the inadvertent taking of an endometrial biopsy in a conception cycle is not associated with an increased rate of miscarriage. This would imply that the remaining endometrium is not disrupted and, therefore, that the observed fragmentation of the Gynocheck biopsies cannot be attributed to the prior taking of a curette biopsy. Gynocheck is designed so that its arms sweep as much of the uterine cavity as possible, and it may be that this mechanism fragmented the endometrium.

The three outpatients were between 28 and 33 years of age and were all nulliparous. Perhaps it is not surprising that they tolerated Gynocheck less well than the women reported previously who were older and presumably in the main parous.

In conclusion, Gynocheck did not obtain specimens suitable for use in infertility and was poorly tolerated.

Acknowledgments

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Development of a modified bivalve speculum for donor insemination

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In many infertility clinics, donor insemination (DI) is performed using a Cusco's bivalve speculum to inspect the cervix. The instrument is usually inserted upside down with the upper blade placed posteriorly within the vagina since this avoids the handle striking the examination couch when the blades are opened. The volume of semen used is usually 0·5 ml (two straws of 0·25 ml each).

After placement of the semen at the external cervical os there is a tendency for some to overflow and collect in the cupped posterior lip of the speculum. Despite careful manipulation of the instrument, some of the semen is lost by being spread further down the vagina or by remaining

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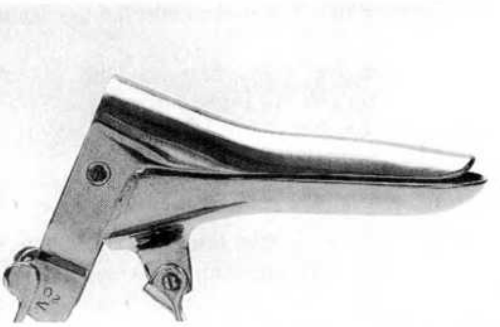

Fig. 1. The upper blade, which is usually inserted posteriorly, has been flattened and shortened. When the blades are closed, this blade recesses within the concavity of the cupped blade therefore facilitating insertion.

in the posterior blade upon removal of the speculum.

Since the initial volume used is very small, loss should be minimized and the maximum possible volume of semen left in the posterior fornix in contact with the cervix.

To achieve this, a simple initial modification of a bivalve speculum was made, such that the concavity at the end of the posterior blade was flattened. As a result no cupping existed where semen might collect and the flattened blade allowed the semen to drain off into the posterior fornix.

The instrument was prepared by Bolton Instruments Ltd, Unit 3, Nutwood Trading Estate, Sheffield, UK.

A comparative study was then carried out to assess semen loss with the Cusco's speculum and with the new instrument.

Patients and methods

Fifty consecutive women receiving DI were recruited, each of whom had two treatments on successive days. For the initial 25 women the Cusco's speculum was used on the first day and the modified instrument on the following day; for the next 25 women the order was reversed.

After insertion of the speculum and inspection of the cervix, insemination was performed with the tip of the inseminator at the external cervical os. The speculum was then removed and any direct loss in the speculum or at the introitus noted and recorded on pre-designed sheets. The patient was asked to indicate if any discomfort occurred during insertion of the instrument, localization of the cervix or at the time of removal.

Results

Semen loss was noted to occur more often with the Cusco's speculum (in 14 of 50; 28%) than with the modified speculum (in 4 of 50; 8%) and this difference was statistically significant ($\chi^2 = 6{\cdot}7$, $P<0{\cdot}01$).

However, the new instrument caused discomfort during insertion in more women than was found with the Cusco speculum, 29 compared with 14; ($\chi^2 = 9{\cdot}1$, $P<0{\cdot}01$). There was no discomfort when the blades were opened to locate the cervix, or during removal. As a result, the instrument was further modified (Fig. 1) to achieve the following.

(1) The flattened blade was slightly shortened and made to recess within the concavity of the cupped blade when in the closed position.

(2) The angle of the racheted arm was altered to prevent contact with the mons pubis.

This newer speculum was then assessed in another 20 women in the same manner as before and it was found to be as effective as the initial modification in preventing semen loss but insertion and removal was much easier.

Conclusion

A modified bivalve vaginal speculum has been designed which acts to prevent loss of semen when the instrument is removed during DI treatment. It would be valuable at this stage to assess its effect on success rates by means of a long-term study.

Acknowledgments

The authors would like to thank Dr Sheila Cooke and the nurses of the University Research Clinic, Jessop Hospital for Women, for their support.

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Alterations in bladder volume and the ultrasound appearance of the cervix

G. C. Mason *Research Fellow,* M. J. A. Maresh, *Consultant Obstetrician, St Mary's Hospital for Women and Children, Manchester M13 0JH*

Ultrasound inspection of the cervix in pregnancy has been used in an attempt to predict cervical incompetence and preterm delivery. It is known that ultrasound estimations of cervical lengths increase with increasing bladder volumes, particularly if the bladder is overdistended. To overcome this problem the technique of using a 'full bladder with care to avoid overdistension' has been described. The main reason behind this apparent lengthening lies in the fact that a variety of external markers (Mahran 1980; Brook *et al.* 1981; Parkinson & Wilson 1986; Constantini *et al.* 1986) have been used to locate the internal os, so that its position depends on the relation of the bladder to the lower uterine segment and cervix.

The present study quantifies the effect of alterations in bladder volume on ultrasound observed cervical length, using an internal marker for the internal os.

Subjects and methods

The study included 31 parous women in the second trimester of pregnancy who had at least three ultrasound cervical assessments, usually on consecutive days (maximum time interval 10 days). Fifteen of them had had a previous preterm delivery and 16 had had a term delivery. They were asked to attend with a full bladder. On each occasion the cervix was assessed by G. M. using a GL Z series sector scanner.

The external os was taken at the point where a line drawn through the canal would bisect another line drawn tangentially to the anterior and posterior cervical lips. The internal os was considered to be located at the superior aspect of the cervical canal at the interface between canal and decidual lining of the uterine cavity in an attempt to be representative of the histological internal os as described by Aschoff (1905).

Measurements were obtained with a 3·5-MHz probe, the image being frozen when the internal and external os and canal were all visible (Fig. 1). The procedure was repeated until three consecutive consistent measurements were obtained and this result was recorded. Afterwards the voided bladder volume was measured. Several of the women were scanned again after voiding to ensure complete emptying and one woman with a significant residual volume was excluded from further study.

Machine accuracy was confirmed to within 1 mm with a tissue phantom. An analysis of covariance was performed on the data, on the assumption that the regression slopes for the individual subjects would have been parallel if greater numbers of observations had been obtained. Approval for the study was obtained from the District Ethics Committee.

Results

There was a marked variation in voided volumes not only between, but also within, individuals on

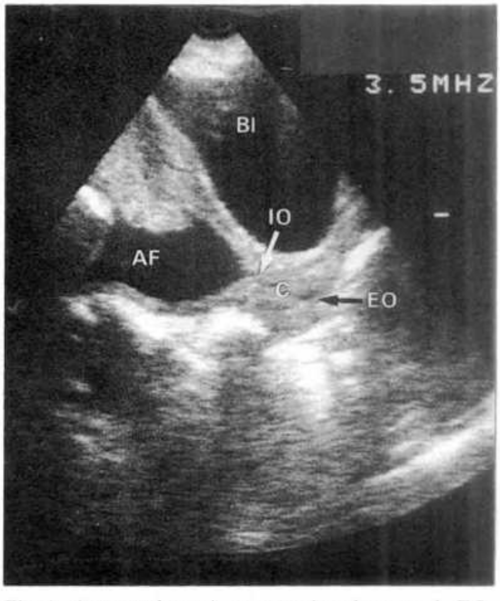

Fig. 1. A normal cervix as seen by ultrasound. EO, External cervical os; C, cervical canal; IO, ultrasound internal os; BI, Bladder; AF, amniotic fluid.

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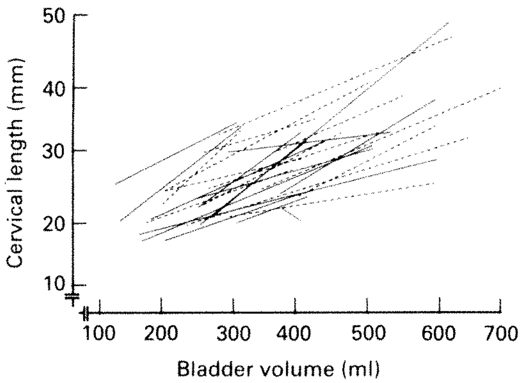

Fig. 2. Regression lines of bladder volume against cervical length measured by ultrasound, for 30 parous women in the second trimester. Women with a previous preterm delivery (----); women with a previous term delivery (—). The length of the line indicates the range of bladder volume for the individual woman.

different occasions. Regression lines for the results of individual women are plotted in Fig. 2, the length of the line indicating the range of bladder volume. Of the 30 women 29 demonstrated an increase in cervical length with increasing bladder volume, which occurred throughout the bladder volume range and not just with overdistension. The slope of the common regression line (0·039 ± 0·0053) is statistically significant ($P<0{\cdot}001$).

Discussion

There is apparent linear cervical lengthening with increasing bladder volume. This is unlikely to be due to cervical compression since the cervix is composed predominantly of fibrous tissue (Danforth 1947). Compression of the lower segment could make the cervix appear longer, but in this study the use of a technique which locates the internal os accurately should have avoided this. It is most likely to have occurred secondarily to alterations in the angle of the cervix from the vertical to the horizontal plane, a similar phenomenon being noted with fetal femur measurements (Abramowicz & Jaffe 1988). The same effect can occur with a vaginal probe if the bladder is not always empty.

Changes in the cervix suggestive of preterm delivery have almost certainly been misdiagnosed in the past due to failure both to locate the internal os accurately and to allow for bladder volume. Furthermore partial compression of the lower segment can give the impression of a partially dilated endocervical canal with protrusion of the membranes. The role of ultrasound in the diagnosis of cervical incompetence and the possibility of preterm delivery therefore remains unclear.

Acknowledgments

The study was supported by a grant to G.M. from the North West Regional Health Authority. We thank Miss L. Hunt for statistical advice.

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BIRTH

ISSUES IN PERINATAL CARE AND EDUCATION

Edited by **Madeleine H. Shearer** RPT

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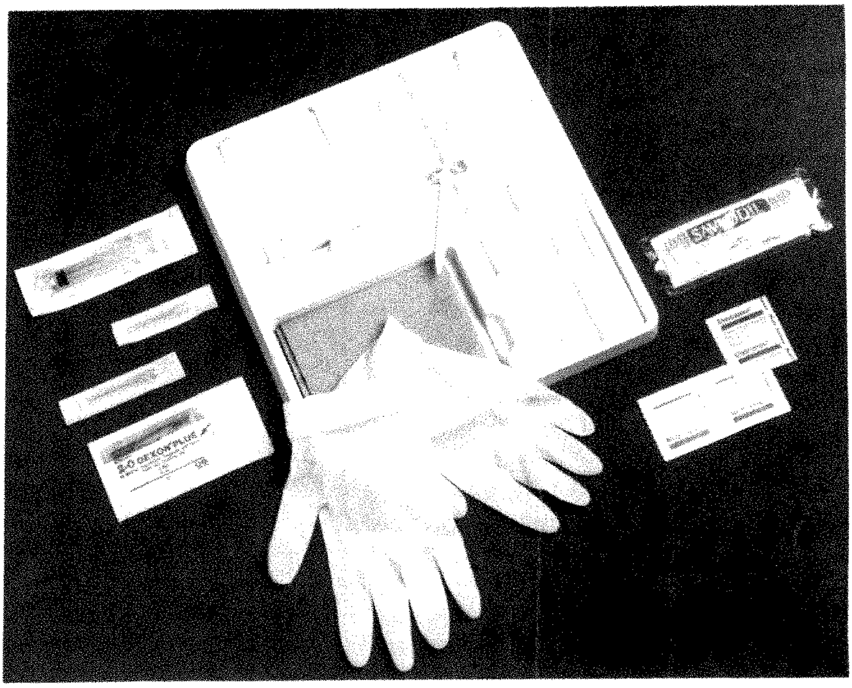

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CORRESPONDENCE

Planned trial of transcervical resection of the endometrium versus hysterectomy

Dear Sir,

Let us suppose that a new drug has been developed to treat dysfunctional uterine bleeding (DUB) and let us call that drug TCRE. Before its general use would be permitted let alone encouraged it would have to undergo careful and controlled, and preferably randomized, trials to compare its efficacy and side effects with other drugs currently in use for DUB, and be approved by the Committee of Safety of Medicines.

Drug therapy is only one of a series of interventions available to us as clinicians. Surgery is another. Why is it, therefore, that attitudes towards the assessment of these two types of intervention are so different? Randomized controlled trials of new surgical procedures *vs* the alternatives are virtually unknown in gynaecology. I would suggest that this is not only unscientific but also unethical.

There is an intervention called TCRE (otherwise transcervical resection of endometrium) for DUB described by De Cherney *et al.* (1987) and Magos *et al.* (1989) and discussed by Macdonald (1990) in his useful commentary on 'modern treatment of menorrhagia'. Although endometrial ablation is an attractive potential alternative to hysterectomy the two have never been compared. The new techniques have been developed and promoted by enthusiastic skilled surgeons without the same constraints as are imposed on our pharmaceutical colleagues.

The 'gold standard' treatment for DUB is hysterectomy and endometrial ablation needs to be compared with that in a randomized controlled trial as advocated by Magos *et al.* (1990). The fact that it may be difficult does not lessen the need for, or obligation on us to do so. Once that comparison has been carried out, various ablative techniques can be compared with each other.

Macdonald (1990) calls for long-term follow-up studies. These are not sufficient. Surgery must be placed under the same constraints as other interventions and tested properly. We have embarked on a randomized controlled trial of TCRE *vs* hysterectomy in this unit funded by the local Research Committee of the South West Regional Health Authority.

We would be delighted to widen the study to include other centres if they would like to join us.

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BOOK REVIEWS

Implantation: Biological and Clinical Aspects edited by Michael Chapman, Gedis Grudzinskas and Tim Chard. Springer Verlag, London, Berlin, Heidelberg, New York, 258 pages with figures and tables, £60.00

The title of this book raised hopes of new insights into implantation—an area of reproductive physiology where frontiers of knowledge are advancing rapidly as a result of the new understanding brought about by *in vitro* fertilization. A glance at the index brings disappointment. Very few of the 18 sections are at all concerned with implantation. The book had its genesis in a meeting held three years ago at Guys Hospital. Stimulating meetings do not necessarily make good books. The conference was held at the right time for research workers to compare findings and views, but too soon for a concensus to take shape. Faced with the awful permanence of print, many took refuge in updated versions of previously published material. Not that overviews of their work by pioneers such as Elisabeth Lenton and Steve Bell are not apropos.

This book is weakest in the clinical part of its subtitle, where many of the contributors appear to be straining to discern clinical applications ahead of understanding. The biological sections stand up better. A notable example is the review of his work on platelet activating factor (PAF), another of those ubiquitous sets of mysterious initials by Chris O'Neil. The story he tells is fascinating; a pity he wanders from his own terrain into speculative discursions about immunosuppressive factors and EPF (the impending demise of this concept makes it unnecessary to remember that EPF stands for early pregnancy factor). The publications from the Sydney school since the meeting have established the importance of PAF and it is gripping to read the story of the first realization that this phosphocoline derivative plays a definitive part in human implantation.

Although Michael Sinosich makes no real effort toward the improbable exercise of demonstrating a role for pregnancy-associated plasma protein A (PAPP-A, yet another set of those initials which make scientific reading a burden), his essay on Fact, Fiction, and Future in PAPP-A research gives a fascinating glimpse of a scientific quarrel in our time. He is on sound ground. His demonstration of elastase inhibition by PAPP-A points the way toward explaining the control of trophoblast penetration.

There are 18 titles in this slim volume. The works range from a three page snippet on hPL and SP1 (more initials) by Tim Chard to a 38 page overview of PAPP-A by Sinosich. The topics include pituitary and ovarian hormones, placental hormones and proteins, endometrial proteins, prostaglandins, reproductive immunology, and a hopeful section on possible clinical applications of these. The book is fascinating to those working on embryo-maternal signals but incomprehensible to the uninitiated.

Arnold Klopper

No Fault Compensation in Medicine edited by Ronald D. Martin & John Harvard. Royal Society of Medicine Ltd, London, 1989, 290 pages with figures and tables. Available through booksellers or Hoddle Doyle Meadows Ltd, Old Mead Road, Elsenham, Bishop's Stortford, Herts CM22 6JN, £20.00

As the demands for compensation for perceived medical negligence increase on an exponential basis, there is an urgent need for informed discussion on how to meet this problem and to review the processes of civil tort as they apply to medical accidents. For this reason this book, which reports the proceedings of a conference on no fault compensation, is well-timed and provides a basis for further debate.

In a way, it makes singularly depressing reading. There are very few contributors to this book of 19 chapters who are actively in practice. Furthermore, there are no factual data about the pattern of claims within the United Kingdom and it is disappointing that this information is not available because it is central to making realistic decisions about the future. Although there are discussions about the Swedish and New Zealand systems of no-fault compensation, it would have been valuable to have had some observations on the malpractice scene in the United States of America, if only because they have extensive information on the effect of litigation on clinical practice. This would surely have put the alternatives to no-fault compensation into perspective.

The proposals put forward by the British Medical Association do not specifically address the most important issue in litigation and that is the problem of brain damage and in particular, birth related injuries. If this one factor was removed from the equation, nearly all other problems could be met by the traditional legal processes. By opting for a blanket scheme, the costs may be politically unacceptable.

Perhaps the concept of 'no fault compensation', a term that carries perjorative overtones, should be abandoned and a scheme of patient insurance introduced in line with the proposals made by the Birth-Related Injuries Compensation Act in West Virginia.

For those readers who wish to acquaint themselves with the various aspects of the debate about compensation and medical injuries as it stands at the present time, this book is useful and informative. For anyone looking for solutions to these problems, they are unlikely to find the answers in this volume.

E. M. Symonds

The New Our Bodies and Ourselves. The Boston Women's Health Book Collective. British edition edited by Angela Phillips and Jill Rakusen. Penguin Books Ltd, London, 1989, 716 pages with figures and tables, £12.99 soft cover.

You may feel that you already know that obstetricians are lower than slime and only just one point above nuclear deterrents in the feminist Hall of Fame, but, by God, this book doesn't half confirm it. Having said that, and if you can bear an experience akin to overdosing on Jill Tweedie, Our Bodies, Ourselves contains much to commend it. Firstly, it represents wonderful value—716 pages full of information for £12.99. Secondly, it does have some terrific chapters—on breast cancer for instance, on contraception, and also on abortion where the use of first person accounts within the text is particularly effective. Each chapter has a very full list of references ('resources' in women's collective-speak) and the book covers not just women's health, in the conventional sense but also other areas such as food, ageing, mental health, rape and 'The politics of women and medical care' (which will send most consultants scuttling for the blood pressure tablets but which might be instructive as a set text for medical students). The chapter on sexuality is excellent and it is refreshing to find that this chapter covers the needs of the disabled.

There are one or two areas which cause raised eyebrows—for instance, the recommendation that 'a woman's first smear test should be followed by a second test, six to twelve months later to confirm the negative result' because of the 'large minority of false negative results'. One does not dispute that there are false negatives but if every woman had a repeat smear, to check a negative result of her first test, one shudders at the thought of the extra burden this would impose on an already creaking system—readers will be frightened.

Perhaps this book ought to be sold with a health warning for obstetricians—'Injurious to professional pride'—this might prevent apoplexy in one or two consultants. Otherwise, it is a very useful book.

Vivienne Parry

Ovarian Pathology (Current Topics in Pathology) Vol. 78 edited by Francisco Nogales. Springer Verlag, Berlin, Heidelberg, 1989, 180 pages with figures and tables, DM 148

There are eight contributors to this book on selected aspects of ovarian pathology. Despite the international reputation of the authors the quality of the contributions is not uniformally high. The chapters on the prognostic significance of pathological features in ovarian carcinoma and the concept of borderline malignancy in ovarian tumours are to be recommended. In contrast it seems inappropriate to include in the chapter on the individual and integrative roles of the oncologist and pathologist in managing ovarian cancer non-epithelial tumours and tumours of borderline malignancy in a discussion of the behaviour of adenocarcinoma of the ovary. It is unusual and interesting to find a section on ovarian tumours in laboratory and domestic animals and helpful to have an overview of non-neoplastic disease of the ovary.

It is disappointing that, in a book published in 1989, one chapter contains published references only up to 1986. When contributions are received, by an editor, over a period of time, it is essential that writers are given the opportunity to update their references. The book is generally very well-referenced and I suspect that these differences reflect the time at which chapters were submitted for publication.

There are irritating inconsistencies in terminology, which probably reflect the individual preference of the contributors but which cannot account for the use, in one paragraph, of both chorioncarcinoma and choriocarcinoma. The reader may also be confused by the use of terms 'malignant implants' and 'metastatic deposits' in relation to disease in the serosa of a woman with a tumour of boderline malignancy.

The book is probably aimed at pathologists rather than gynaecologists and is too selective to become a standard text but it may prove useful as a starting point for anyone wanting an overview of the subject.

G. H. Buckley

Books received some of which may be reviewed at a later date.

Principles and Practice of Clinical Gynecology. Second Edition edited by N. G. Kase, A. B. Weingold and D. M. Gershenson. Churchill Livingstone, New York, Edinburgh, London, 1990, 1056 pages, fully illustrated, £60.00

The Uterine Circulation (Reproductive and Perinatal Medicine X) edited by Charles R. Rosenfeld. Perinatology Press, Ithaca, New York, 1990, 312 pages with figures and tables, list price $104.50 (Prepaid discount price $84.00)

Perinatal Hematology (Methods in Hematology) edited by Blanche P. Alter. Churchill Livingstone, New York, Edinburgh, London, 1990, 265 pages, 70 illustrations, £40.00

Adipose Tissue and Reproduction (Progress in Reproductive Biology and Medicine 14) edited by R. E. Frisch. Karger, Basel, 1990, 142 pages with figures and tables, £58.00, US$92.75

Premenstrual, Postpartum and Menopausal Mood Disorders edited by Laurence M. Demers, John L. McGuire, Audrey Phillips and David R. Rubinow. Urban & Scharzenberg, Baltimore, Munich, 224 pages with figures and tables £33.00

Obstetric Emergencies (Contemporary Issues in Emergency Medicine) edited by Guy I. Benrubi. Churchill Livingstone, New York, Edinburgh, London, 1990, 250 pages with figures and tables, £29.95

Functional Diagnostics of the Lower Urinary Tract by A. Tanko. Akadenai Kiado, Budapest, 1990, 205 pages, fully illustrated, £24.00

Advances in Fetal Physiology: Reviews in Honor of G. C. Liggins (Research in Perinatal Medicine VIII) edited by P. D. Gluckman, B. M. Johnston and P. W. Nathanielsz. Perinatology Press, Ithaca, New York, 1989, 424 pages with figures and tables, $102.50 (Prepaid discount price $82.00)

Development of Circadian Rhythmicity and Photoperiodism in Mammals (Research in Perinatal Medicine IX) edited by Steven M. Reppert. Perinatology Press, Ithaca, New York, 1989, 262 pages with figures and tables, $102.50 (Prepaid discount $82.00)

Quadruplets and Higher Multiple Births (Clinics in Developmental Medicine No 107) by Marie M. Clay. Mac Keith Press, London, 1990, 186 pages with figures and tables, £20.00

Assessment & Care of the Fetus. Physiological, Clinical and Medicolegal Principles edited by Robert D. Eden and Frank H. Boehm. Prentice-Hall, Hemel Hempstead, 1990, 1043 pages with figures and tables, £52.75

The Politics of Maternity Care: Services for Childbearing Women in Twentieth-Century Britain by Jo Garcia, Robert Kilpatrick and Martin Richards. Clarendon Press, Oxford, 1990, 346 pages. Paperback £9.95, Hardback £32.50

Acupuncture in Gynaecology and Obstetrics by Royston Low. Thorsons Publishing Group Ltd Wellingborough, Northants, 1990, 128 pages fully illustrated with line drawings, £20.00

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COMMENTARIES

Detrusor instability—current management

Continence is an acquired phenomenon. Under normal circumstances, we learn to voluntarily inhibit our detrusor contractions when we are 'potty trained' during infancy and thereafter the majority of us will have stable bladders for the rest of our lives. An unstable bladder is one that is shown objectively to contract, spontaneously or on provocation, during the filling phase while the person is attempting to inhibit micturition (ICS 1987).

Although many different causes for this condition have been proposed, the underlying pathophysiology remains a mystery. A certain proportion of individuals with unstable bladders actually have an underlying neurological cause and the term detrusor hyper-reflexia is reserved for these circumstances. However, for the majority, no underlying cause is ever found so they have 'idiopathic detrusor instability'. This is a common condition possibly occurring in up to 10% of the adult population. Both men and women may be affected but the problem for women is often worse because their relative urethral sphincter weakness allows the common symptom of urgency to become urge incontinence.

Treatment is difficult, as in the majority of cases, there is uncertainty whether detrusor instability is due to a central or a peripheral abnormality. The currently available therapies aim either to re-establish central control or to alter peripheral (detrusor) innervation. Many forms of treatment have been tried, but none has been universally successful.

It is important, before treatment, to exclude other reasons for the symptoms as there are numerous different causes of urgency and frequency of micturition—the two most common symptoms in individuals with detrusor instability. Once an accurate diagnosis has been made using urodynamic methods, adequate explanation should be given to the patient regarding the underlying pathophysiology. It may be that understanding and reassurance are all that is required. However, most patients wish for more active treatment. Initially, medical management is appropriate and the choice lies between behavioural modification and pharmacological intervention.

Behavioural modification

The rationale behind this type of treatment is that since suppression of detrusor contractions is learnt in childhood, then it should be possible to re-acquire control during adult life. The following types of bladder re-education have been tried:

1. Bladder drill.
2. Biofeedback.
3. Hypnotherapy.
4. Acupuncture.

Bladder discipline was initially described by Jeffcoate & Francis (1966) and the technique of bladder drill was popularized by Frewen in the 1970s. The modified form described by Jarvis (1989) is outlined below and appears to be an easy and fairly successful schedule to follow.

1. Make an accurate urodynamic diagnosis of detrusor instability.
2. Exclude pathology.
3. Admit to hospital.
4. Explain rationale to patient.
5. Instruct to void by clock, not by desire.
6. Increase voiding intervals by 30 min after each successful day.
7. Maintain a normal fluid intake.
8. The patient keeps her own fluid balance chart.
9. Reinforce motivation by commenting positively when there is improvement.
10. Encouragement from other patients, nurses and medical staff.

Biofeedback (Cardozo *et al.* 1978) and hypnotherapy (Freeman & Baxby 1982) achieve the same goals as bladder drill but are more time-consuming for the patient and the operator. The advantage of any form of behavioural intervention is that the morbidity and mortality of surgery and the side-effects of drugs are avoided.

The success rates (cured or improved) for all these types of treatment is initially about 80% but unfortunately there is a significant relapse rate. For those with mild to moderate detrusor instability, behavioural intervention may produce a complete and lasting cure and this is obviously desirable. However, for many, symptoms recur when they return to their normal environment and life-style and may not respond to further bladder drill. Severe idiopathic detrusor instability, and detrusor hyper-reflexia, do not respond well to this type of treatment which should not be attempted as it will waste time and cause unnecessary distress.

Pharmacological intervention

Drugs are still the mainstay of treatment for detrusor instability. In current clinical practice, most of the drugs described fall into one of the following categories:

1. Anticholinergic agents.
2. Musculotrophic relaxants.
3. Tricyclic antidepressants.
4. Calcium channel blockers.
5. Antidiuretic hormone analogues.

Anticholinergic agents act by producing competitive blockade of acetylcholine receptors at the post-ganglionic parasympathetic receptor sites. Atropine, the classical anticholinergic agent, cannot be used because of its side-effects, but propantheline (Probanthine) may help symptoms, especially frequency of micturition, if given in high enough doses (often in excess of 45 mg three times daily). It produces the usual anticholinergic side-effects of dry mouth, blurred vision, drowsiness, constipation and tachycardia. However, it is inexpensive and is worth trying but must be instituted slowly. Emepronium bromide (Cetiprin), which was used for many years in the management of urgency and urge incontinence, has recently been withdrawn from the market in the UK, although it is still available as emepronium carrageenate (Cetiprin novum) in other parts of Europe.

The musculotropic relaxants cause smooth muscle relaxation and may have an effect on other organs apart from the bladder. The side-effects are essentially anticholinergic. Flavoxate hydrochloride (Urispas) has been a popular drug in this category for a number of years but there is no evidence that it is more effective than placebo when administered either orally or parenterally (Briggs *et al.* 1980).

Oxybutynin chloride is widely used in the USA but in the UK can only be prescribed on a named patient basis. It was probably the first truly effective drug available for the treatment of detrusor instability. The recommended dose is 5 mg three times daily but this may be increased if the side-effects are not intolerable, or decreased for the elderly. Unfortunately, the side-effects may be severe, with a very dry mouth and a bad taste occurring in up to 80% of patients (Cardozo *et al.* 1987). However, for many sufferers from detrusor instability, it provides relief from symptoms.

The tricylic antidepressants have a mixed pharmacological action. They are anticholinergic, sympathomimetic and have a central sedative effect. Imipramine has long been prescribed for nocturnal enuresis in children and is particularly useful for nocturia and nocturnal enuresis in adults. Its side-effects are anticholinergic together with fatigue and tremor. The normal dose is 50 mg at night and it can be combined with propantheline during the day for those women who suffer from diurnal and nocturnal frequency of micturition.

Calcium channel blockers are the latest group of pharmacological agents to be tried in the treatment of detrusor instability. They were originally developed for use in cardiovascular disease and limit the availability of the calcium ions that are required for the contractile process. They have some anticholinergic effects as well and their side-effects are basically anticholinergic. Terodiline has recently become popular in the UK and throughout Europe and may be given in a dose of up to 25 mg three times daily, although less should be prescribed for the elderly. From clinical trials and in practice it would appear to be helpful, particularly for the symptoms of urgency and urge incontinence (Tapp *et al.* 1989).

The synthetic antidiuretic hormone analogue (DDAVP) has been shown to reduce nocturnal urine production when given intranasally as snuff or spray in a dose of 20–40 μg at night (Hilton & Stanton 1982). Obviously this cannot be used for diurnal symptoms as well, but it has recently been shown to be safe long term and is one of the few really helpful preparations for adult noctural enuretics (Knudsen *et al.* 1989).

It is often difficult for the prescribing clinician to decide which drug to try for which patient. For those women whose main symptoms are urgency or urge incontinence, I think that the initial choice lies between oxbutynin and terodiline.

Oxybutynin is preferable for women who would rather not take tablets continuously but who are prepared to tolerate quite severe side-effects. Alternatively, I would opt for terodiline in those women who are prepared to take tablets on a regular basis (as terodiline does not reach its maximum effect for up to 2 weeks after the start of treatment) but who are not prepared to tolerate such severe side-effects. If diurnal frequency is the main symptom, I would try propantheline and for those with nocturia I would give imipramine initially and DDAVP if that does not work.

In addition, peri- or postmenopausal women are often helped by some form of oestrogen replacement. This will not cure the underlying bladder problem but has been shown to raise the sensory threshold of the bladder and to ease such symptoms as nocturia (Fantl *et al.* 1988). Oestrogens will also make postmenopausal women feel generally well and therefore they will be better able to cope with their other problems.

Surgical treatment

For those women in whom neither behavioural intervention, nor drug therapy, nor a combination of both produces sufficient improvement in symptoms, there are many surgical procedures available. The current data regarding transvesical phenol injections are mixed and although this treatment gained initial popularity for the treatment of detrusor hyper-reflexia and detrusor instability that was resistent to medical treatment (Blackford *et al.* 1984), it is now considered to be less effective and to be associated with more complications than was thought previously (Rosenbaum *et al.* 1988).

The 'clam' augmentation enterocystoplasty is currently the most widely used operation and is worth considering for those women who have intractible detrusor instability that has failed to respond to simple forms of treatment (Mundy & Stephenson 1985). Women must be warned, however, that they may be swapping their incontinence for voiding difficulties and some will need to perform clean intermittent self-catheterization after the operation. There is also the problem of mucus production from the gut segment and the possibility of neoplastic change when urine is in contact with gut mucosa for a long period of time.

For the elderly and chronically disabled, surgery is not usually indicated and it may be more appropriate to consider long-term catheterization, with an anticholinergic agent if catheter bypassing is a problem. The provision of an adequate continence service with the help of a continence adviser, advice on incontinence pads, garments and availability of laundry facilities, is also important.

For most female patients detrusor instability represents a 'nuisance' rather than a major disability; but women need help when symptoms, particularly urge incontinence, become a major inconvenience. The same form of treatment will not be suitable for all sufferers and it is worth remembering that detrusor instability is a disease of spontaneous exacerbations and remissions, so treatment may only be required when symptoms are at their worst. Treatment must be tailored to suit the individual as the symptoms which are most troublesome for one patient may not be the worst for another. Drug regimens may need to be changed as different types of therapy become less effective or the patients' main symptoms change. Although it is rarely possible to cure detrusor instability completely, it is nearly always possible to improve the quality of life of the sufferer.

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Gynaecology and the National Confidential Enquiry into Perioperative Deaths

Obstetricians are well acquainted with national audit. The Confidential Enquiry into Maternal Deaths has published triennial reports since the 1950s: reports which have exhaustively reviewed maternal mortalities and have made important recommendations for the future. There is no doubt that these have improved obstetric care and led to enhancement of the facilities available in maternity units and delivery suites. Perinatology has recently adopted this concept of confidential, anonymous peer review, and important regional studies have highlighted shortcomings in provision and training for those who care for the newborn; again, this audit process is shown to facilitate improved patient outcomes. Anaesthetists participated in numerous audits of their practice over a similar period. However, surgeons and gynaecologists, specialities intimately related to anaesthesia, were not involved directly at least until 1985. In 1985 a proposal to create a Confidential Enquiry into Perioperative Deaths (CEPOD) by the Association of Anaesthetists of Great Britain and Ireland received support from the Association of Surgeons of Great Britain and Ireland. All the Royal Colleges of Surgeons and the Royal College of Obstetricians and Gynaecologists then agreed to promote this enterprise, which started with pilot studies in three districts, and then continued as a major review of all perioperative deaths in three national health service regions. The Nuffield Provincial Hospitals Trust and the King's Fund provided financial backing.

CEPOD studied all deaths which occurred within 30 days of surgery in the Northern, South Western, and North East Thames health regions. Over one calendar year, 1986, all deaths were reported by local reporters and investigated by peer review. The experiment was an overwhelming success. Over the study period 4034 deaths were reported relevant to 485 850 operations. The peer investigation of these deaths by a panel of assessors revealed no new facts but quantified many well-known anecdotes. The assessors and the steering group for the study made recommendations that there was a need for assessment of clinical practice on a national basis and that regular local self audit should be a routine part of clinical behaviour. The recommendations went on to suggest that supervision of trainees should be improved, that undertaking emergency and urgent surgery on more than one hospital site should cease, that consultants should not stray out of their field of expertise, and that management of co-morbidity and resuscitation of the very ill are critical components of surgical practice and take time if they are to be effective.

National CEPOD was born from this initial experience. NCEPOD is supported by the Royal College of Obstetricians and Gynaecologists who have nominated a member of the steering group. NCEPOD plans a rolling programme over 5 years to sample different categories of patients who come to surgery, to review the management of surgical and gynaecological patients and to make recommendations about the delivery of clinical care. NCEPOD has concentrated on surgery for children under 10 years of age in 1989. This year, 1990, NCEPOD will investigate a random selection of all perioperative deaths in adults. The dead patients will be matched with a patient who undergoes similar surgery and survives, the patient to be randomly chosen from another region. All the data will be scrutinized anonymously and confidentially and no original patient or consultant-specific data will be published. NCEPOD has already set up a system to report relevant deaths from every district in England, Wales, Northern Ireland, Guernsey, Jersey and the Isle of Man. Ministry of Defence establishments and some 40% of the private sector are involved too. Financial support comes from the appropriate health departments and the independent sector.

So what is the gynaecologist's commitment to all this? The NCEPOD office in London does most of the work. We shall send to individual consultants questionnaires about the patients, alive or dead, that are randomly chosen in the sample. Consultant gynaecologists, with the help from their juniors, should complete these questionnaires and return them to us. The analysis will be undertaken by a group nominated by the colleges and specialist associations to do the task. Details of all this and the names of the specialists were sent to all gynaecologists in December 1989.

National audit should help to identify problems and remedy them, and lead to improved clinical outcomes for patients. However, it will only be a success if all participate and if the recommendations are put into practice. The Confidential Enquiries into Maternal Mortality have already trail-blazed this approach and obstetricians have shown that it works. It is now time to extend this process to gynaecology.

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Should abdominal decompression be consigned to the history books?

Much antenatal care is concerned with trying to diagnose impaired fetal growth. Yet, apart from delivery, there have been surprisingly few suggestions concerning management of the condition. One of the more imaginative approaches has been the attempt to augment blood flow to the uterus by intermittently reducing the pressure about the woman's abdomen. This technique was initially conceived as a method of overcoming the resistance of the abdominal wall to the forward movement of the uterus during labour contractions (Heyns 1959). Physiological studies in South Africa (Heyns *et al.* 1962; Blecher 1968) and the UK (Coxon & Haggith 1971) suggested that the technique was associated with a reduction in intra-uterine pressure and improved uteroplacental blood flow. Several clinical trials were subsequently reported and they indicated that abdominal decompression might improve various measures of growth and perinatal outcome in pregnancies complicated by hypertension or impaired fetal growth (see below).

What captured the public imagination were reports suggesting that routine use of abdominal decompression in normal pregnancy could promote the baby's intellectual development (Heyns 1962). This possibility was considered of such importance that the South African Minister of Health called for an independent assessment of the technique by the National Institute for Personnel Research. Women who attended the antenatal clinic at the Queen Victoria Maternity Hospital in Johannesburg before 30 weeks gestation, and who agreed to participate in the study, were randomly allocated to a group asked to attend for abdominal decompression thrice weekly, and a control group asked to attend antenatal physiotherapy classes instead (Liddicoate 1968). The women completed intelligence tests before allocation. Their offspring underwent developmental testing at 4 weeks, 9 months and 3 years of age. Although contact was retained with only 44% of the children until three years of age, the groups available for examination remained comparable in terms of the mothers' intelligence scores.

The developmental scores of the children from the abdominal decompression group were slightly higher than those of children from the control group, but these differences were not statistically significant. Analysis of unstructured observations made by the assessor, who was 'blind' to the grouping of the children, revealed that mothers in the decompression group frequently gave manifestly unrealistic accounts of their children's achievements. In addition, their children were significantly more likely to display undisciplined or aggressive behaviour than those in the control group. It is at least possible that temperamental differences between the two groups of children resulted from altered, perhaps more permissive, child-rearing practices among the parents who believed that abdominal decompression had conferred superior intelligence upon their children. Publicity given to techniques before their benefits have been confirmed by properly controlled trials may make it impossible for such trials subsequently to distinguish between the effects of the technique and those arising from the expectations of the participants. A recent review of the original hospital records of a substantial proportion of the participants in this study by Liddicoate (1968) revealed no differences between the groups with respect to birthweight and Apgar scores (Hofmeyr *et al.* 1990).

Should this saga be consigned to the history books as an irrelevant aberration in the development of our speciality? It may be that unrealistic claims concerning the beneficial effects of abdominal decompression on uncomplicated pregnancies have diverted attention away from possible benefits of the technique for the relief of labour pain and fetal distress, and the treatment of hypertension and poor fetal growth. The last two problems may be associated with impaired blood flow to the placenta, and there is no well-validated method of increasing placental blood flow. Blecher & Heyns (1967) studied 80 women with pre-eclampsia, essential hypertension or chronic nephritis. Varma & Curzen (1973) studied 140 pregnancies with ultrasound fetal biparietal diameter measurements below the 10th centile. In both studies allocation to abdominal decompression treatment was by alternation, and the frequency of low birthweight was reduced (typical odds ratio 0·22, 95% CI 0·14 to 0·34). Macrae *et al.* (1971) randomly allocated 28 of 56 women with low urinary oestriol levels and clinical evidence of impaired fetal growth to receive abdominal decompression. The mean birthweight was 2800 (SD 591) g compared with 2296 (SD 364) g for the controls. Meta-analysis of the three studies showed a statistically significant reduction in perinatal mortality (typical odds ratio 0·36, 95% CI 0·19 to 0·67) (Hofmeyr 1989).

These studies may have been biased and their results cannot be regarded as conclusive. But given the paucity of options for managing fetal growth retardation, their positive results should not be ignored. Physiological studies using Doppler ultrasound and well-controlled clinical trials in compromised pregnancies are needed to prove or disprove the tantalizing possibility that abdominal decompression may be an effective treatment for impaired fetal growth.

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Birth asphyxia and the intrapartum cardiotocograph

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Summary. The intrapartum cardiotocographs (CTGs) of 38 severely asphyxiated, term infants, born during a 17-month period, and those of 120 healthy term infants acting as controls were independently reviewed by three investigators who were unaware of the clinical outcome. Interobserver agreement was good (Kappa statistic = 0·74, P<0·0001). The investigators found that cardiotocographic abnormalities were present in 33 of the asphyxiated infants (87%) and in 35 of the controls (29%) and predicted that the abnormalities were severe enough to lead to significant fetal metabolic acidosis at delivery in 23 asphyxiated infants (61%) and in 11 controls (9%). The differences between the two groups were highly significant (P<0·001). Using the traditional diagnostic criteria for fetal distress, the investigators found that fetal blood sampling was indicated in 58% of cases in the asphyxia group and in 20% of controls but was only performed in 16% of asphyxiated infants and in 8% of controls. Furthermore, the median response times of delivery suite staff for abnormal fetal heart rate patterns were similar whether the FHR changes, classified using Krebs' CTG scoring system, were moderate or severe: 80 min and 90 min, respectively. These findings suggest that interpretation of the intrapartum CTG continues to pose major problems for practising obstetricians.

Continuous electronic fetal heart rate (FHR) monitoring in labour has become an integral part of obstetric practice since its introduction in the 1960s (Steer 1982) despite the fact that no clear evidence exists for its efficacy, especially in low-risk pregnancy. A study by Sykes *et al.* (1983) in a major UK teaching hospital showed that the use of the intrapartum cardiotocograph (CTG) for predicting low pH at birth was poor and the authors called for more frequent and sensible usage of fetal blood sampling (FBS) until better methods of intrapartum fetal monitoring become available. It was subsequently suggested that poor prediction might be due to failure of interpretation rather than failure of the technology (Steer 1986; Van Den Berg 1987).

Any benefit from continuous CTG monitoring must depend on the ability of midwives and obstetricians in the delivery unit to interpret very complex and confusing FHR patterns and

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to use them to decide the best clinical management. We have, therefore, analysed current use of the intrapartum CTG in a unit where more than 6000 infants are born annually and approximately 50% of labours are assessed by continuous CTG monitoring. We compared the intrapartum CTGs in a group of women (>37 weeks gestation) delivered of infants who were asphyxiated at birth with a control group of similar women delivered of normal infants, and compared the management of CTG abnormalities in the two groups We also examined closely the relation between birth asphyxia and the intrapartum CTG.

Subjects and methods

A retrospective study of the intrapartum CTGs from both asphyxiated and healthy, term infants was carried out over a 17-month period at the John Radcliffe Hospital Maternity Department in Oxford. The diagnosis of birth asphyxia was based on recorded clinical findings of a low Apgar score, umbilical artery metabolic acidosis, the need for intermittent positive pressure ventilation, meconium aspiration or subsequent convulsions. Cases in the asphyxia group were chosen from a register compiled by the neonatal staff of 85 term infants admitted to the special care unit, each of whom had a diagnosis of birth asphyxia recorded. Because many of these infants had multiple indications for admission to the unit a careful review of each case was made by a neonatologist and only those cases in whom birth asphyxia was the primary diagnosis were included in the asphyxia group. Therefore, 21 of these 85 infants were excluded because pathology other than asphyxia was judged to be more important in determining the infant's condition at birth and subsequent course. Reasons for exclusion included trauma, infection, metabolic derangements and congenital fetal abnormality. Of the remaining 64 infants, 26 were excluded because they did not have continuous monitoring in labour, having been classified as low-risk. A further four were excluded because the CTGs were unsuitable for analysis (see later). After these exclusions there remained 38 infants in the asphyxia group.

Table 1 provides the information, the specific combinations of factors, used by the neonatologist in deciding which babies were included in the asphyxia group. Apgar scores were available for all babies and cord blood measurements for 34. All the infants in the asphyxia group were depressed at birth: the median Apgar score was 3 (range 0–6). Of the 38 infants 16 (42%) had an Apgar score <7 at 5 min, and 22 (58%) required intermittent positive pressure ventilation for >5 min. Twenty-one (55%) demonstrated signs of central nervous system irritability such as increased tone, staring, fisting, cycling and a high pitched cry and seven (18%) had frank convulsions. Three infants suffered from meconium aspiration syndrome.

Umbilical artery blood acidosis (pH <7·20) was recorded in 32 infants and a further two showed capillary blood acidosis immediately after delivery. Of the 38 infants 26 (68%) had an umbilical artery blood pH<7·12 combined with a base deficit of >12 mmol/l (1 SD below mean-Sykes *et al.* 1983) and 17 (45%) had a pH<7·04 combined with a base deficit of >17 mmol/l (2 SD below mean).

A control group of 128 infants was obtained by selecting two monitored cases, one immediately before and one immediately after the 64 cases in the original asphyxia group. The fact that some of the controls were selected on either side of

Table 1. Criteria used by the neonatologist to allocate 38 infants to the severe asphyxia group*

Code	Number of infants
a+b+c+d	11
a+b+c	8
a+b+d	5
a+b	3
a+b+e	2
a+b+c+e	2
a+b+c+d+f	2
a+b+c+d+e	2
b+d+e	1
b+c+f	1
a+b+c+f	1
Total	38

a: Umbilical artery or capillary blood pH at birth <7·20.

b· Apgar score <7 at 1 min.

c: Intermittent positive pressure ventilation.

d Signs of cerebral irritability—cycling, fisting, staring.

e Clinical convulsions treated with anticonvulsant drugs.

f: Meconium aspiration syndrome.

* All infants had been admitted to the special care unit because of birth asphyxia

asphyxia cases that were subsequently excluded because they did not have a CTG should not affect the validity of the control group since this was not a true case-control study with matching of the cases but rather, a group of controls which represented the hospital population of monitored labours, and excluded cases of asphyxia admitted to the special care unit. Random selection would have been adequate for this control group. The indications for monitoring ranged from the presence of any antenatal risk factor to the development of intrapartum complications such as meconium staining of amniotic fluid or the need for oxytocin augmentation.

Eight of the control cases were subsequently excluded because loss of signal quality resulted in recordings with less than 20 min of interpretable data. This has not been appreciated at the time of collection. Therefore, the final control group comprised 120 cases.

The 158 CTGs from the asphyxia and control groups were independently reviewed by three investigators (KWM, PJ, RP) who were unaware of the clinical outcome. A fourth member of the perinatal team (VR) prepared the CTG's for assessment by obliterating patient details, dates and any references to outcome.

CTGs were classified into three groups: A, B and C. Traces were allocated to group B when two or more of the three observers agreed that the CTG was sufficiently abnormal to indicate intervention in the fetal interest (FBS or operative delivery) using the criteria shown in Table 2, or when a suspicious recording (possible or probable FHR abnormality present) was of poor quality (signal loss, artefact or an absent tocograph) but no attempt was made to use a fetal scalp electrode to improve the recording. CTGs were allocated to group C when they were so abnormal that at least two observers predicted (correctly or incorrectly) that the umbilical artery blood would show a metabolic acidosis, with $pH<7\cdot12$ and base deficit $>12\cdot0$ mmol/l, at delivery (1 SD below mean: Sykes *et al.* 1983). The CTGs in this group showed combinations of abnormalities such as baseline tachycardia, late decelerations and reduced baseline variability (see results section). All other traces were allocated to group A.

Recordings were only included if they were >20 min and continued to within 40 min of delivery. Both external recordings obtained by ultrasound and internal recordings obtained from a fetal scalp electrode were included. Tracings were examined in consecutive 20 min sections so that the investigators' decisions to intervene were based on information similar to that which was available to the clinician on duty. CTG's from the first and the second stages of labour were analysed separately. FHR abnormalities in first stage labour were an indication for FBS while similar patterns in the second stage were usually an indication for early delivery. However, FBS after full cervical dilatation was indicated if a spontaneous vaginal delivery was permitted despite prolongation of the second stage and an abnormal FHR pattern.

The criteria for intervention in the fetal interest, outlined in Table 2, were chosen arbitrarily by the three observers. Authoritative guidelines for response times for particular FHR patterns do not exist in the literature so that the times chosen by the observers constituted their own consensus of safe response times. The CTG

Table 2. Indications for intervention in the fetal interest (fetal blood sampling or operative delivery) agreed by all three investigators

Fetal heart rate abnormality	Duration (min)
Uncomplicated tachycardia: 160–180 bpm	120
Uncomplicated tachycardia: >180 bpm	60
Bradycardia: <100 bpm	20
Moderate variable decelerations >50 bpm, >30 <60 s	120
Severe variable decelerations >50 bpm, >60 s	40
Late decelerations (lag time >20 s)	40
Reduced baseline variability: <5 bpm	60
Complicated tachycardia: FHR >160 bpm, late or moderate/severe variable decelerations and reduced baseline variability	40

bpm = beats/min.

scoring system described by Krebs *et al.* (1979) was used when the response times of staff for CTG abnormalities were measured.

Details of procedures and interventions were obtained from the case records. A low Apgar score was defined as $\leqslant 3$ at 1 min. A low pH (acidosis) was defined as a pH$<$7·12 together with a base deficit $>$12 mmol/l, except where otherwise specified. Clinical convulsions were included if they occurred within 48 h of birth and required treatment with anticonvulsant drugs. Follow-up of asphyxiated infants depended upon the severity of the initial insult and subsequent neonatal progress but in all suspect or abnormal cases a full neurological assessment was performed at age 1 year.

Statistics

χ^2-test with Yates' correction was used to compare results in the asphyxia and control groups. The Mann-Whitney *U*-test was used to compare response times. Differences were considered significant at the $P<0{\cdot}05$ level.

Results

Table 3 shows the obstetric characteristics of the study group (n=38) compared with the control group (n=120). During the study period, approximately 50% of all obstetric patients at the John Radcliffe Hospital were monitored in labour, and the control group therefore represents this monitored population, excluding all cases of birth asphyxia requiring admission to the special care unit.

Predictive value of the intrapartum CTG

The overall agreement on the need for FBS in the first or second stage of labour was 89% between observers 1 and 2, 91% between observers 2 and 3 and 89% between observers 1 and 3 (n=158). The need for FBS was agreed upon by all three observers in 38 cases, by two observers in 12 and was considered necessary by a single observer in a further 12. Inter-observer agreement was also measured using the Kappa statistic: Z=12·4, K=0·74, $P<0{\cdot}0001$.

Umbilical artery blood acidosis, defined as pH$<$7·12 plus base deficit $>$12 mmol/l, was predicted (correctly or incorrectly) from the CTG by all three observers in 30 cases, by two observers in 12 and by a single observer in 16. The overall agreement for the prediction of acidosis (and its absence) in umbilical artery blood was 87% between observers 1 and 2, 94% between observers 2 and 3, and 89% between observers 1 and 3. The predictions of acidosis were correct in 65%, 72% and 73% of cases in which a measurement was made for observers 1, 2 and 3, respectively. The Kappa statistic for inter-observer agreement in this case was also calculated: Z=9·77, K=0·74, $P<0{\cdot}0001$.

In Tables 4 and 5 the asphyxia and control groups have been amalgamated since this was the way that the investigators reviewed all the CTGs. A strong association is shown between cardiotocographic abnormality and poor fetal outcome (Table 4). The CTG was classified as abnormal (groups B and C) in all seven infants who had neonatal convulsions and in 18 of the 21 infants born with both acidosis and a low Apgar score. However, there were three instances where a 'normal' (group A) CTG was associated with subsequent acidosis and a low Apgar score in the infant. One was associated with cord prolapse after CTG monitoring was discontinued. In the second, the tracing was discontinued 20 min before the birth of the infant, only in the third was the CTG classified as 'normal' right up until the birth of the infant.

Table 5 shows the values for sensitivity and specificity of a group C CTG classification to identify fetuses at risk of asphyxia in this population of 158. CTGs from group C (n=34) typically showed severe bradycardia or combinations of abnormal FHR patterns. Using the following four categories: (i) tachycardia-FHR>160 bpm, (ii) late or severe variable decelerations, (iii) reduced baseline variability <5 bpm and (iv) severe bradycardia <100 bpm, there were 15 group C CTGs which showed three or more FHR abnormalities, nine with two FHR abnormalities and 10 with a single FHR abnormality. Nine of the ten cases with a single FHR abnormality had severe bradycardia. FHR abnormalities were present for at least 40 min in the first three categories and for at least 20 min in the fourth category.

Sensitivity was highest when a group C CTG was used to predict a combination of acidosis and low Apgar score at delivery (81%) and lowest when used to predict acidosis alone (58%) while the specificity remained comparable at 85% and 86%, respectively. Missing data on cord blood values had little effect on the predictive value of a group C CTG for infants born

Table 3. Obstetric characteristics of the study group compared with the control group

	Severe asphyxia (*n*=38)	Controls (*n*=120)
Primiparae	32 (84·2%)	72 (60·0%)**
Antenatal complications	23 (60·5%)	49 (40·8%)
Induction of labour	17 (44·7%)	53 (44·2%)
Pethidine in labour	16 (42·1%)	38 (31·7%)
Epidural anaesthesia	23 (60·5%)	67 (55·8%)
Oxytocin	19 (50·0%)	67 (55·8%)
Meconium	15 (39·5%)	21 (17·5%)*
ODFD	18 (47·4%)	18 (15·0%)***
Birthweight <10th centile	3 (7·9%)	12 (10·0%)
Apgar score <4 at 1 min	24 (63·2%)	4 (3·3%)***
Cord pH: Mean (SD)	7·01 (0·15) (*n*=34)	7·23 (0·09)*** (*n*=62)

ODFD: operative delivery for fetal distress. $^{*}P<0{\cdot}05$, $^{**}P<0{\cdot}01$, $^{***}P<0{\cdot}001$.

with both acidosis and a low Apgar score since only three out of a total of 28 infants with a low Apgar score at delivery did not have cord measurements (ie 89% of the severely depressed infants in this study had cord blood measurements). Even if all three had been incorrectly predicted this would only have reduced the sensitivity from 81% to 71%. On the other hand, the missing data would be expected to have a greater effect on the prediction of acidosis alone.

Table 4 shows that there were two neonatal deaths from asphyxia in the group C CTG group. One resulted from an acute placental abruption in labour and the other from delayed extraction of the aftercoming head of a breech. Also, follow-up at 1 year of age showed that three infants had severe neurological impairment, one from group B and two from group C. The first had developmental delay and hypotonia (group B CTG) (although subsequent follow up at 2 years of age revealed that the hypotonia was benign and that the developmental delay was secondary to poor environmental circumstances). The second and third infants had spastic quadriplegia and severe developmental delay.

For completeness, it should be added that during the 17-month study period, in the 26 cases with no CTG in labour (from the original group of 64 asphyxiated infants), six infants had seizures, one infant had cerebral palsy at 1 year of age and one infant died from the effects of birth asphyxia.

Clinical significance of an abnormal CTG

Table 6 compares the frequency of abnormal cardiotocography in the asphyxia and control groups. Some type of cardiotocographic

Table 4. The relation between cardiotocographic classification and fetal outcome

CTG classification	Low Apgar	Cord pH measured	Low cord pH	Low cord pH and low Apgar	Seizures	NND	CNS abnormal at 1 year
Group A (*n*=90)	4	36	9	3	0	0	0
Group B (*n*=34)	3	29	8	1	2	0	1
Group C (*n*=34)	21	31	23	17	5	2	2
Totals (*n*=158)	28	96	40	21	7	2	3

Apgar scores were recorded in all infants and cord pH measurements in 61%. Low Apgar is a score <4 at 1 min, low pH is an umbilical artery blood pH <7·12 plus a base deficit >12 mmol/l.
NND = neonatal death
CNS = central nervous system.

Table 5. The value of a group C CTG in predicting a poor fetal outcome

	Predicted outcome					
CTG classification	Low Apgar		Low pH		Low Apgar and low pH	
	Yes	No	Yes	No	Yes	No
Group C	21	13	23	8	17	14
Groups A and B	7	117	17	48	4	61
Total	28	130	40	56	21	75
Sensitivity	75·0%		57·5%		81·0%	
Specificity	90·0%		85·7%		85·3%	

Apgar scores were recorded in all infants (n=158) and cord pH measurements in 96 (61%). Low Apgar is a score <4 at 1 minute, low pH is an umbilical artery pH<7·12 plus base deficit >12 mmol/l.

abnormality (group B+C tracings) was present in 33 asphyxiated infants (87%) compared with 35 controls (29%) (P<0·001). The abnormality was considered severe (group C tracings only) in 23 asphyxiated infants (61%) and in 11 controls (9%) (P<0·001). Although this might appear to be a good method of detecting birth asphyxia, extrapolation of these results to all term infants (> 37 weeks gestation) who were monitored in labour during the 17-month study period (n=3688) would mean that the obstetrician would have been presented with a total of 1077 group B+C tracings of which only 34 (3·2%) resulted in the infant being admitted to the special care unit for asphyxial problems. Similarly, although 338 group C tracings would be expected over the same period only 23 of these (6·8%) resulted in the infant being admitted to the unit. However, all the major complications (less one seizure) in Group C occurred when a low pH and Apgar score followed birth.

Intervention for fetal distress

In the investigators' opinion, using the criteria shown in Table 2, FBS was indicated in 57·9% of the asphyxia group and in 20% of the controls but was performed in only 15·8% and 8·3% of these two groups, respectively. Some intervention in the interest of the fetus was required, in the investigators' opinion, in 87% of the asphyxia group and 29% of the control group but FBS or operative delivery (or both) were actually performed in only 42% of asphyxiated infants and in 21% of controls (Table 6).

Although more operative deliveries for fetal distress (ODFD) were performed in the asphyxia group than in the control group (Table 3, P<0·001), for those with abnormal cardiotocography the frequency of operative deliveries was similar in the two groups (Table 7). The proportion of operative deliveries was also similar for those with group B and group C tracings in Table 7.

Delivery suite staff 'response times'

In Table 8 the delivery suite staff response times for abnormal FHR patterns were considered. These response times give some indication of the staff's ability to interpret the intrapartum CTG. Response time was measured from the time of onset of the abnormal FHR pattern until FBS or ODFD were performed, the abnormal FHR pattern resolved or spontaneous delivery occurred. Some abnormal patterns resolved following the use of intrauterine resuscitation: oxygen administration by mask, changing to the left lateral position or discontinuing oxytocin. To enable a valid comparison of response times for abnormal FHR patterns between the asphyxia and control groups it was necessary (a) to consider separately cases of acute, sustained bradycardia (FHR<100, duration >5 min) and (b) utilize a

Table 6. The investigators' CTG classification and a comparison between the optimal and the actual rate of intervention in the asphyxia and control groups

First + second stage labour	Severe asphyxia (n=38)	Controls (n=120)
Group B CTG	10 (26·3%)	24 (20%)
Group C CTG	23 (60·5%)	11 (9·2%)***
FBS indicated	22 (57·9%)	24 (20·0%)***
FBS performed	6 (15·8%)	10 (8·3%)
FBS and/or ODFD performed	16 (42·1%)	26 (21·7%)*

ODFD· operative delivery for fetal distress. *P<0·05, **P<0·01, ***P<0·001

Table 7. Operative delivery for fetal distress (ODFD) in the asphyxia and control groups in the presence of an abnormal FHR pattern—CTG groups B and C*

	Severe asphyxia (n=38)		Controls (n=120)	
CTG	n	ODFD	n	ODFD
Group B	10	4	24	12
Group C	23	13	11	5
Total	33	17	35	18

*Only two operative deliveries for fetal distress were performed in CTG Group A.

CTG scoring system so that only patterns of similar severity were being compared. Krebs' CTG scoring system (Krebs *et al.* 1979) was employed for this purpose (Table 9). CTGs scoring 0–4 were very abnormal (n=23) and all came from the original group C tracings. Those scoring 5–8 (n=35) came mainly from group B tracings (94%). The score assigned to a particular tracing was applicable for the full duration of the response time recorded in Table 8.

Response times for CTGs with a Krebs' score 0–4 were not significantly different from those with a score of 5–8 (Mann-Whitney U test, $P>0{\cdot}05$). This was true for both the asphyxia and control groups. The same observation was made when the asphyxia and control groups were combined in order to increase the numbers: the mean and median response times in the Krebs' 0–4 score group (n=23) were 128 (SD 100) and 90 min, respectively, compared with 91 (SD 61) and 80 min in the Krebs' 5–8 score group (n=35), (Mann-Whitney U test, $P>0{\cdot}05$). A cumulative distribution of these response times is shown in Figure 1.

The mean response time for sustained bradycardia in the asphyxia group (n=7) was 27 (SD 10) min compared with 14 (SD 4) min in the control group (n=3). This result was significant: Mann-Whitney U test, $P<0{\cdot}05$.

In the three infants with a severe neurological deficit at 1 year of age the intrapartum CTG, in one case, was only moderately abnormal (Krebs' score 6), the response time 45 min, Apgar scores: 4/10; cord gases not measured This mother also had a history of a previous neonatal death. In the second case, a vasa previa led to fetal haemorrhage and the response time to the abnormal FHR pattern (Krebs' score 2) was 90 min. At birth the Apgar scores were 3/6 and umbilical artery pH 6·94. In the third case, the significance of a very abnormal tracing (Krebs' score 2) was not recognized for almost 8 h. At birth the infant's Apgar scores were 0/1 and umbilical artery pH 6·68.

The response times for the two infants who died were 60 min for the breech and 17 min for the placental abruption. In both the tracings were abnormal but other clinical factors were more important in determining perinatal outcome.

Discussion

Delivery suite staff 'response times'

This review of intrapartum cardiotocography suggests that better use could be made of the information provided by continuous FHR monitoring. As might be expected, abnormal, intrapartum FHR patterns occurred with greater frequency and severity when the infant was asphyxiated at birth. The response times for the CTGs of these asphyxiated infants were not significantly shorter than those for the controls despite the increased severity of the FHR changes. Even more important was the finding that a severely abnormal CTG, scoring 0–4 on the Krebs' system, was not associated with a shorter response time than a moderately

Table 8. Staff response times for abnormal (Krebs' score 5–8) and very abnormal (Krebs' score 0–4) FHR patterns in the asphyxia and control groups*

	Response time (min)									
CTG Krebs'	Severe asphyxia (n=27)					Controls (n=31)				
score	No.	Mean	(SD)	Median	Range	No.	Mean	(SD)	Median	Range
0–4	16	118	(100)	80	50–475	7	145	(94)	120	35–260
5–8	11	71	(26)	70	30–120	24	99	(69)	95	10–270

*Normal CTGs (original group A, n=90) and cases of acute, sustained bradycardia (n=10) were excluded

Table 9. Krebs' scoring system for internal FHR monitoring For each of the listed criteria 0 to 2 points may be given so that a score of 0 to 10 may be obtained

FHR score	0	1	2
Baseline rate (bpm)	<100 >180	100–119 161–180	120–160
Baseline variability (bpm)	<3	3–5	6–25
Oscillations/min	<3	3–6	>6
Accelerations/30 min	0	1–4	>4
Decelerations	Late or severe/atypical variable	Mild or moderate variable	Early decelerations

abnormal one scoring 5–8, when the asphyxia and control groups were combined. One would expect an earlier response to the more ominous patterns as was indeed the case when acute bradycardia was recognized.

Are these response times too long? In a study on long term handicap and the quality of intrapartum care, Niswander *et al.* (1984) considered that failure to act within 90 min of the onset of late FHR decelerations constituted a suboptimal reaction In a previous publication the same author recorded mean response times of up to 151 min for similar FHR patterns although the inclusion of 'flat' tracings makes direct comparison difficult (Haesslein & Niswander 1980). Keegan *et al.* (1985) allowed 30 min for staff to recognize an abnormal FHR pattern and an additional 30 min for them to react to it. Fleischer *et al.* (1982) showed that it took 115 min in the case of late decelerations and 145 min in the case of variable decelerations for 50% of fetuses to develop acidosis in labour.

Our response times of 80–100 min might be considered acceptable if all abnormal FHR patterns were equally ominous. However, the results of our own 'blind' interpretation of these CTGs suggest that it is possible to identify most of the severely affected infants during labour (Tables 4 and 5) and it is, therefore, of concern that the mean response time for all CTGs scoring 0–4 on the Krebs' system (from both the asphyxia and control groups) was still >100 min. The fact that operative delivery for fetal distress was performed in approximately half of these cases whether the CTG was in group B or in group C, together with the response times above, suggests that it was difficult for the staff to discriminate between abnormal and very abnormal FHR patterns.

Obviously, a great variety of clinical factors may influence the response time for an abnormal FHR pattern: observer experience, clinical workload and staffing level at the time; availability and reliability of recording equipment; the patient's ability to tolerate an invasive procedure like FBS at a stressful time; progress in labour; and finally the presence or absence of other clinical signs of fetal distress. It is not possible to judge the appropriateness or otherwise of the response time in an individual case without

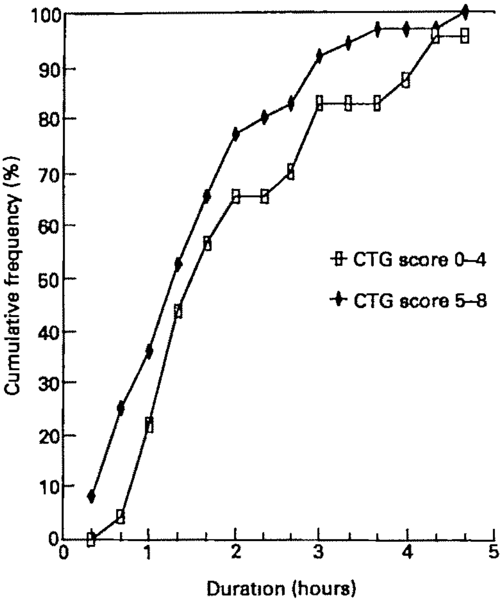

Fig. 1. Cumulative distribution of delivery suite staff response times to very abnormal FHR patterns (Krebs' score 0–4, $n=23$) and to abnormal patterns (Krebs' score 5–8, $n=35$) showing similar response curves. Cases of acute bradycardia have been excluded ($n=10$).

careful consideration of such factors. It would also be unwise to assume that our response times of 80–100 min are unduly prolonged in the absence of comparable data from similar units.

Fetal blood sampling

This review also raises a number of questions about the use of FBS as an adjunct to FHR monitoring in labour. During the study period the hospital FBS rate was approximately 4·0%, reflecting a rate of about 8% among monitored patients since only 50% of the population is monitored continuously in labour and FBS is virtually confined to this group. The sampling rate in the control group was 8·3% and although this matched the hospital rate for monitored patients the reviewers found that FBS was indicated in 20% of this group using the criteria shown in Table 2. Although operative delivery for fetal distress was performed in some of the cases where FBS was indicated, delivery was often delayed, judging by the rather long response times.

The FBS rate in this hospital has remained static over the past 7 years (Hospital Report 1988). Data on FBS rates throughout the UK do not exist at the present time but we believe that few UK delivery units exceed a sampling rate of 8–10%. This implies that few centres in the UK comply with the criteria in Table 2. Most of the abnormal FHR patterns in this study were ominous, comprising patterns that were decelerative or more complicated

In other units, where the FBS rate is similar to our own, staff response times to abnormal FHR patterns may also be longer than expected. The all important question is whether the response time should be shorter when the CTG is severely abnormal. Our data show that if FBS were confined to those with group C tracings, the overall FBS rate would not be increased but the CTG criteria for fetal blood sampling would be significantly changed. In this study, only one third of control cases with a group C tracing had FBS in labour.

Although the overall numbers in this study are small and some of the data are incomplete, we believe that they reflect the current status of intrapartum fetal monitoring at this centre. In one centre in Berlin, all women are monitored in labour and the FBS rate is over 20% (Van Den Berg *et al.* 1987). This FBS rate closely matches the FBS rate anticipated by the reviewers in our control group of monitored patients. Differences in interpretation of the intrapartum CTG must account for much of this additional fetal blood sampling and it is difficult to believe that it does not provide a wider margin of safety for the fetus. It could be argued, therefore, that sampling rates lower than this can only be considered safe if they are accompanied by very skilled interpretation of the intrapartum CTG (Clark & Paul 1985).

Relation between abnormal CTG and fetal outcome

The nature of the relation between an abnormal CTG and fetal outcome may explain some of the difficulties encountered when large numbers of patients are monitored. Although a large proportion of the clinically asphyxiated infants born during the study period had an abnormal CTG in labour (87%), the actual number was only 33. Extrapolating from our control group, in which 29% had an abnormal CTG in labour, to all patients *monitored* during this period, 1077 abnormal CTGs would be expected. This high rate of false positives (low specificity) is responsible for much of the present dissatisfaction with CTG monitoring. Of course it is always difficult to determine the effects of intervention for an abnormal CTG and it is possible that many more asphyxiated infants would have been born if abnormal CTGs in the control group had not been acted upon. On the other hand, spontaneous delivery may have occurred in many of these cases before the fetus sustained any serious injury.

Conclusions

Of clinical and medicolegal importance is the fact that a low umbilical artery pH at birth alone is not a useful guide to subsequent postnatal outcome. The umbilical artery pH of the infants in this study with clinical asphyxia at birth (mean pH 7·01, n=38) was no different to that of all those infants in the study of Sykes *et al.* (1983) with a pH 2 SD below the mean (mean pH 7·02, n=28) who have subsequently been found to have normal neurological development at 4·5 years of age (Dennis *et al.* 1989). A meaningful definition of birth asphyxia must include an objective assessment of intrapartum fetal distress, the infant's condition at birth and neonatal performance and outcome. Without this, the assessment of any antenatal or intrapartum contribution to subsequent outcome remains uncertain.

We have found a strong association between abnormal intrapartum cardiotocography, low pH and Apgar score at birth, and poor postnatal outcome Events in labour appear to have contributed to the outcome in two infants with severe neurological sequelae at 1 year of age The combination of group C CTGs, response times of >90 min, early neonatal convulsions and the subsequent pattern of neurological disability in the second and third infant described, suggests that the injury to these fetuses was sustained during the intrapartum period. Although there is a growing body of opinion that antepartum factors may be more important than intrapartum factors in the aetiology of long term neurological morbidity (Paul *et al.* 1986; Perkins 1986); our findings do not agree with the conclusions from a previous study in this hospital that suboptimal intrapartum care does not relate to postnatal neurological handicap (Niswander *et al.* 1984). Our results provide a warning against complacency in the diagnosis and management of fetal distress in labour and indicate the need for improved intrapartum fetal surveillance.

The intrapartum CTG, properly used, is a sensitive indicator of fetal compromise but its poor specificity must be improved by appropriately timed scalp sampling in carefully selected cases. The fact that experience does matter in the interpretation of the CTG is particularly important. Therefore, it would seem that there are two immediate options: to improve our interpretation of the intrapartum CTG or to more than double our current FBS rate. Certainly, until such time as our CTG interpretation is optimum, we should increase our FBS rate. Attendance at regular, in-service CTG meetings should be mandatory for all staff involved in fetal monitoring. The planned installation of centralized video display units in the delivery suite, able to show continuous and trend displays of the CTG, may help by increasing the general level of expertise and awareness and by facilitating online teaching. Computerized analysis of the intrapartum CTG is another attractive prospect (Pello *et al.* 1988). The fact that trained, well-motivated staff at this centre may not have utilized fully the information available is a strong argument in favour of a more objective method of intrapartum CTG interpretation.

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The efficacy and tolerance of mifepristone and prostaglandin in first trimester termination of pregnancy

UK MULTICENTRE TRIAL

Abstract

Objective—To investigate the use of oral mifepristone (RU 486) and vaginal gemeprost for the induction of legal first trimester abortion.
Design—An uncontrolled multicentre observational study.
Setting—13 Hospital gynaecological units in Scotland and England.
Subjects—588 Pregnant women with up to nine weeks amenorrhoea having legal abortions.
Interventions—Oral mifepristone 600 mg followed 48 h later by vaginal gemeprost 1 mg. Women stayed in the hospital for a minimum of 4 h on each occasion.
Main outcome measures—Frequency of complete abortion and the need for subsequent surgical evacuation, analgesia and blood transfusion.
Results—There was complete abortion in 94% (95% CI 92—96%). None of the 46 women at <43 days gestation needed surgical evacuation. This was performed in 6·5% of the remainder but among these the rate did not increase with gestation. Five women (four from one centre) required both curettage and blood transfusion. A fall in haemoglobin concentration of 2–4 g/dl occurred in only 1%. Narcotic analgesia was required after gemeprost by 37% of nullipara and 13% of multipara. Overall 26% had vomiting and 13% diarrhoea.
Conclusion—The sequential use of oral mifepristone and vaginal gemeprost is effective in inducing abortion up to the 63rd day of pregnancy. Efficient management of pain and bleeding is easier if women are in a hospital for some hours after the gemeprost.

Although in world terms UK abortion rates are low, over 160 000 induced abortions are carried out annually on British women (Editorial, 1988). Vacuum aspiration is the most widely used method in the first trimester, and although it is accepted that the complication rate is low (Tietze, 1981), it is nonetheless a surgical procedure, usually carried out under general anaes-

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thesia, and requiring skilled training. A number of attempts have been made to develop non surgical methods of early pregnancy termination, and these have usually involved prostaglandins or their analogues (Karim *et al.* 1977; Smith & Baird, 1980; Bygdeman, 1984; Cameron & Baird, 1988). In some studies complete abortion rates of 90% have been reported, but the use of prostaglandins has been limited by the occurrence of troublesome, particularly gastrointestinal, side effects.

Mifepristone (RU 486; 17 ß-hydroxy-11ß-(4-dimethylaminophenyl - l) - 17α (prop - 1 - ynyl)-estra-4, 9-dien-3-one); Roussel Laboratories Ltd) is a potent antiprogestogen which, by its ability to block the action of progesterone on the pregnant uterus, provides another approach to drug induced termination of pregnancy. It is a synthetic norsteroid which acts reversibly at the molecular level of receptor binding, having a high affinity for the progesterone receptor (Baulieu, 1985). The drug also has antiglucocorticoid activity (Moguilewsky & Philibert, 1985), but clinical trials have not revealed signs and symptoms of adrenal insufficiency at doses required for its antiprogestogen activity (Spitz *et al.* 1989). There is also weak anti-androgenic (Philibert *et al.* 1985), but no anti-oestrogenic or antimineralocorticoid activity.

The success of mifepristone used alone in inducing abortion has been extremely variable but has never been more than 88% (Kovacs *et al.* 1984; Shoupe *et al.* 1986; Cameron *et al.* 1986; Couzinet *et al.* 1986; Editorial, 1987; Grimes *et al.* 1988) and its use has been complicated by occasional heavy bleeding (Couzinet *et al.* 1986; Editorial, 1987; Grimes *et al.* 1988; Bygdeman & Van Look, 1988). However, the combined use of mifepristone with a small dose of prostaglandin has proved much more effective and there are now a number of reports which testify to the efficacy of mifepristone used in combination with intramuscular sulprostone (PGE_2 analogue) (WHO, 1989) and intravaginal gemeprost (PGE_1 analogue) (Rodger & Baird, 1987; Dubois *et al.* 1988). These studies were restricted to gestations of seven and eight weeks respectively.

The purpose of this multicentre study was to assess the efficacy of mifepristone given in combination with gemeprost to terminate pregnancy of up to nine weeks gestation. The results presented are an interim analysis for a larger study of more than 1000 patients.

Subjects and methods

The study was an open, multicentre hospital investigation to assess the efficacy of mifepristone and vaginal prostaglandin in the termination of pregnancy up to nine weeks amenorrhoea. Women received a single oral 600 mg dose of mifepristone followed 48 h later by a 1 mg vaginal pessary of gemeprost (16,16, demethyl-*trans*-Δ^2 prostaglandin E_1 methyl ester; May and Baker, UK). Women were reviewed over the course of the next four weeks to determine efficacy and tolerance. In each centre permission was obtained from the local ethics committee and termination of pregnancy was agreed under the conditions of 1967 Abortion Act. The intention was that all women would be at least 18 years old and of less than nine weeks gestation. There should have been no previous serious medical or psychiatric disorder, or treatment with glucocorticoid in the previous year. Gestation was assessed from the first day of the last menstrual period and by ultrasound, while viability was confirmed by human chorionic gonadotrophin (hCG) measurement and ultrasound.

Mifepristone tablets were taken in the presence of the investigators after base line data (demography and medical history) and consent had been obtained. All women remained in hospital for 4 h, during which time symptoms, pulse, temperature, blood pressure and blood loss were recorded, and then they were free to go. After 48 h they returned to hospital for assessment and for administration of the prostaglandin pessary. The women remained in hospital under observation for at least 4 h during which time general condition and signs and symptoms of abortion were assessed. Analgesic requirements were also noted. Women left the hospital when the investigators were satisfied that their clinical condition was stable but were requested to return for follow up 7, 14 and 28 days later, at which time efficacy and tolerance were further assessed by history and clinical examination. Women were free to visit the hospital doctor at any time between scheduled visits if necessary. Not all women attended for follow-up.

Results

Over a period of ten months until June 1988, 593 women were recruited from 13 centres (median number of women/centre 46, range 1–99). Two women withdrew after taking mifepristone, one because she had changed her mind (the pregnancy continued to term and a normal baby was born), the other requested surgical termination. Two others vomited shortly after taking mifepristone tablets and were referred for surgical termination. A fifth had an ectopic pregnancy and, although she received mifepristone and gemeprost, eventually required laparotomy and is not therefore included in this analysis.

Patient characteristics

The median age was 24 years, and the range 16–45 years, with 75% in range 18–29 years. Although the intention was to restrict recruitment to women aged ≥18 years, five aged 16 or 17 were treated and have been included. The physical characteristics of the women are given in Table 1.

Of the 588 women, 206 (35%) had at least one previous vaginal delivery, and 130 (22%) had two or more, while 22 (4%) had had at least one caesarean section. One or more miscarriages had been experienced by 44 (7%) and at least 118 (20%) had had one previous termination.

The gestational age at the time of termination is given in Table 2; 70% of women were in the range 43–56 days. Fifteen pregnancies were of gestational age 64–69 days but were included in the analysis.

Efficacy

Of 588 women studied, 580 received the full regimen of mifepristone and gemeprost. Seven aborted with mifepristone alone and did not receive gemeprost for this reason. The eighth did not receive gemeprost, but was recorded as having aborted nine days after mifepristone.

Again of the 588 women, 553 (94·0%, 95% CI 92·1–96%) aborted completely without the need for a subsequent surgical procedure Among the 35 women who had surgical evacuation of the uterus, six had this done around the time of gemeprost administration (four because of haemorrhage and two (one a twin pregnancy) because they did not abort after gemeprost). A further five had curettage following medical termination but before the first (7 day) follow-up, while in the interval 7–14 days a further eight had evacuation, and in the interval 15–28 days, a further 13. Three women had evacuations beyond this period. The usual reason for subsequent evacuation of uterus was suspected retained products. This was usually suspected on clinical grounds but not always confirmed at the time of surgery. Ultrasound scans were not particularly helpful. Of 507 scans at the one week follow-up, 47 suggested retained products, but only nine of these women went on to have a surgical evacuation immediately or later.

Table 1. Characteristics of the women in the study

	Mean	SD	Range
Height (cm)	162·4	6·3	143–182
Weight (kg)	60·6	9·3	42–118
Ponderal index	23·0	3·4	16–50

Only nine women were lost to follow-up before the response could be fully determined. However, in six the investigator thought that abortion was complete before they left hospital (one had not required gemeprost), and two telephoned at the time of their next menstrual period. None of the nine was thought to have a continuing pregnancy, hence all nine were considered as successes.

It was necessary for 159 (27%) women to stay in hospital for longer than 4 h after gemeprost administration, but most had been discharged by 8 h. Fourteen (2%) remained for 9–48 h.

None of the 46 women with gestation <42 days required surgery (Table 2). The rate of evacuation subsequent to this was between 6 and 7% and did not increase with advancing gestation.

Bleeding

Serious haemorrhage, requiring haemostatic curettage and blood transfusion occurred in five women, shortly after gemeprost administration in four and in the fifth during the subsequent few days. The women's own assessment of bleeding

Table 2. Gestation length and number of women requiring surgery

Gestational age (days from LMP)	Number of women *n* (%)	Number requiring surgery *n* (%)
<36	7 (1)	0
36–42	39 (7)	0
43–49	153 (26)	10 (6)
50–56	255 (43)	16 (6)
57–63	119 (20)	8 (7)
63–69	15 (3)	1 (7)
Total	588 (100)	35 (6)

Table 3. Self-reported assessment of bleeding during and following treatment

Women's assessment of bleeding	After mifepristone		After PG		Days following medical termination	
	0–24 h	24–48 h	2 h	4 h	2 days	9 days
None	536 (91)	264 (45)	158 (27)	25 (4)	6 (1)	100 (21)
Light or spotting	30 (5)	181 (3)	225 (9)	203 (35)	187 (35)	320 (70)
Moderate	12 (2)	86 (15)	165 (28)	296 (51)	255 (48)	38 (8)
Severe	1 (0·2)	33 (6)	19 (3)	41 (7)	83 (16)	2 (0·4)
Excessive with clots	3 (0·5)	18 (3)	7 (1)	8 (1)	2 (0·4)	0 (0)
Information missing	6 (1)	6 (1)	6 (1)	7 (1)	0 (0)	0 (0)
Total	588 (100)	588 (100)	580 (100)	580 (100)	533 (100)	460 (100)

The values are numbers of women with percentages in parenthesis. Not all women attended for follow-up after the procedure.

is given in Table 3. In 9% bleeding was described as severe or excessive in the 24–48 h period after mifepristone. A similar rate was reported 4 h after gemeprost. Two days after the procedure 16% noted severe or excessive bleeding but by nine days only 0·4%. Objective assessment of bleeding is given in Table 4 where differences in haemoglobin measurement immediately before treatment and seven days after gemeprost administration are reported (the five women who required blood transfusion were excluded). In 93% of the women there was little or no change (up to 1 g/dl), while in 1% of patients there was a decrease of 2–4 g/dl.

Pain

The women's own assessment of pain is given in Table 5. Twelve (2%) reported severe pain after mifepristone administration and before gemeprost. Two hours after gemeprost administration, 21% reported severe pain but this had decreased to 10% by 4 h. By two days after the termination, 5% of women still complained of severe pain, but none by nine days. The objective assessment of pain is difficult but can be indirectly gauged by the need for analgesia (Table 6). Here there was a marked difference between nulliparous and parous women in the need for narcotic analgesia (37% compared with 13%). About 30% of both groups required non-narcotic analgesia. However, there was a considerable difference in narcotic use between the centres, the range being 8–50%.

Other problems

The major symptoms other than pain or bleeding were vomiting and diarrhoea (Table 7). One quarter of all women had vomiting during the 4 h after gemeprost administion while 13% had diarrhoea.

Discussion

This large multicentre study shows that medically induced termination of pregnancy is a realistic alternative to surgery. Of 588 women, 94% had complete abortion induced without the need for surgical intervention. These results extend previous experience of the combination of mifepristone and prostaglandin both in terms of numbers and gestation. Using a dose of mifepristone 150 mg over four days followed by 1 mg pessary of gemeprost, Cameron & Baird (1988) reported successful abortion in 18 out of 19 women with 35–56 days amenorrhoea. Rodger & Baird (1987) studied 100 women of the same gestation who were given mifepristone 400–600 mg followed by gemeprost, and reported a 95% complete abortion rate. In a recent WHO multicentre trial (WHO, 1989) mifepristone 150–200 mg was given to 250 women with up to 49 days amenorrhoea before an intramuscular

Table 4. Changes in haemoglobin in 521 women who had haemoglobin measured before treatment and 7 days after PG administration

Change in Hb (g/dl)		Women *n*	(%)
Increase or no change		211	(40)
Decrease	0–1	276	(53)
	1·1–2·0	28	(5)
	2·1–3 0	5	(0·9)
	3·1–4·0	1	(0·2)

Table 5. Self reported assessment of pain during and following treatment *n* (%)

Women's assessment of pain	After mifepristone		After PG		Days following medical termination	
	0–24 h	24–48 h	2 h	4 h	2 days	9 days
None	489 (83)	297 (50)	90 (15)	140 (24)	296 (55)	428 (93)
Mild	65 (11)	194 (33)	164 (28)	256 (44)	135 (25)	29 (6)
Moderate	23 (4)	79 (13)	203 (35)	127 (22)	73 (14)	3 (0 7)
Severe	5 (1)	12 (2)	120 (21)	59 (10)	27 (5)	0 (0)
Information missing	6 (1)	6 (1)	3 (0·5)	4 (0·7)	2 (0.4)	0 (0)
Total	588 (100)	588 (100)	580 (100)	580 (100)	533 (100)	460 (100)

The values are numbers of women with percentages in parenthesis Not all women attended for follow-up after the procedure.

injection of sulprostone. Overall 89% of women had a complete abortion, 7% were incomplete and 2% were treatment failures (the outcome could not be adequately determined in a further 2%). However, most of the curettages came from one centre and when this centre was excluded, the authors reported a 94% complete abortion rate, which was similar to a smaller single centre study using the same regimen (Bygdeman & Swahn, 1985). More recently Dubois *et al* (1988) in France have reported a similar success rate.

The two major problems associated with medical termination of pregnancy are bleeding and pain. In the present study severe haemorrhage requiring blood transfusion occurred in five women (1%). This problem has been reported both in regimens which employ mifepristone alone (Kovacs *et al.* 1984, Cameron & Baird, 1988), and also in combined regimens (WHO, 1989). Subjective assessment of bleeding indicated that 9% of women had severe or excessive bleeding in the 24–48 h period following mifepristone administration and a similar proportion in the 4 h after gemeprost administration. After the procedure, 16% complained of severe or excessive bleeding at two days, but only 0·4% by nine days However, objective assessment of blood loss by haemoglobin assessment was more reassuring, and other studies are also reassuring in this respect (Cameron & Baird, 1988; WHO, 1989). A measured blood loss of 72 ml (range 15–398 ml) has been reported in 72 women treated with the same regimen at up to 56 days amenorrhoea (Rodger & Baird, 1987). Further objective studies are required, while detailed acceptability studies should focus on this area. Dubois *et al.* (1988) have reported that the interval between mifepristone and prostaglandin can be reduced to 36 h without loss of efficacy, and this may reduce the occurrence of severe bleeding.

Pain was the other main problem (Tables 5 & 6). During gemeprost administration 28% of women required opiate analgesia. This is higher than other studies reporting combined regimens, 7·6% (WHO, 1989), 9% (Rodger & Baird, 1987), and 16% (Cameron & Baird, 1988), but is much less than with prostaglandin alone (Cameron & Baird, 1988). The reasons for this difference are not clear. However, the present study has highlighted the marked difference in analgesic requirement between nulliparous and parous women. Again there is scope for further study in this area and it might be anticipated that the circumstances of the abortion and

Table 6. Need for analgesia up to 4 h after administration of PG

Analgesia	Nulliparous (*n* = 370)		Parous (*n* = 218)	
	n	(%)	*n*	(%)
Narcotic	137	(37)	29	(13)
Non-narcotic	120	(32)	65	(30)
None	113	(31)	124	(57)
	$X^2 = 51{\cdot}4$, $P<0{\cdot}005$ (2 DF)			

Table 7. Appearance of new symptoms, other than abdominal pain and vaginal bleeding

Symptom	During 4 h after mifepristone (*n* = 588)		During 4 h after PG (*n* = 580)	
	n	(%)	*n*	(%)
Headache	32	(5)	21	(4)
Vomiting	17	(3)	150	(26)
Diarrhoea	3	(0·5)	73	(13)

the attitudes of the attendants might have a strong influence on the need for analgesia.

Other problems were infrequent, although 26% did complain of vomiting in the 4 h after gemeprost administration. The use of smaller doses of prostaglandin and, possibly, different analogues needs to be explored and will no doubt be addressed in future studies.

Thus the efficacy and tolerance of medical as opposed to surgical termination of pregnancy is being increasingly defined. There is a need for more detailed studies of acceptability, but the initial response was very positive (Urquhart & Templeton, 1988), as was apparent in earlier studies of prostaglandin-only methods (Rosén *et al.* 1984). The implications of this development also extend to the organization of the health services. Clearly there will be a saving in operating theatre and anaesthesia time, but the procedure needs to be clinic based, and preferably hospital based, in view of the small but definitive risk of severe haemorrhage. The appropriate facilities need to be developed and the most suitable environment will become evident with increased experience. It cannot be expected that in this country the advent of medical termination will increase access to termination, but the impact in the Third World could be considerable.

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The physiological and clinical effects of progesterone inhibition with mifepristone (RU 486) in the second trimester

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Summary. A double-blind placebo-controlled trial was performed in 20 primigravidae to assess the physiological and clinical effects of oral mifepristone on myometrial contractility and sensitivity in the second trimester. Ten women received 600 mg of oral mifepristone and 10 women a placebo 24 h before abortion was induced in both groups, with extra-amniotic PGE_2 instillation. Intrauterine pressure recordings demonstrated increased spontaneous uterine activity and increased sensitivity to PGE_2 and ergometrine, but no change in oxytocin sensitivity after mifepristone treatment. There were no significant differences in PGE or PGF metabolite concentrations in peripheral maternal plasma over the 24-h study period after treatment between the mifepristone and placebo groups. The mean induction abortion interval in the mifepristone group was 512 (SD 321) min compared with 1128 (SD 606) min in the placebo group ($P \leqslant 0.02$). The mechanism whereby mifepristone provokes enhanced uterine contractility and sensitivity to prostaglandins, with a reduction in abortion times, does not appear to be through endogenous production of PGE or PGF.

Progesterone has an inhibitory effect on pregnant myometrial activity in lower mammals, and progesterone withdrawal is an essential step in the sequence of events preceding labour (Davies & Ryan, 1973). In primates (Walsh *et al.* 1984) and humans (Turnbull 1983) progesterone withdrawal before labour has not been recorded, however, Csapo (1974) proposed that the degree of uterine activity during pregnancy is regulated by the balance between the intrinsic suppressor, progesterone, and the stimulant, prostaglandin.

The effects of progesterone on the myometrium can now be further investigated using the potent new synthetic antiprogesterone steroid mifepristone (RU 486), which blocks progesterone receptors thus causing progesterone withdrawal at a cellular level in the uterus, releasing the myometrium from progesterone control Mifepristone has been shown to increase uterine contractility and sensitivity to prostaglandin analogues in the first trimester (Bygdeman & Swahn 1985; Swahn & Bygdeman 1988), but to

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date no human contractility studies have been performed using this drug in later pregnancy.

The aim of this study was to assess the influence of mifepristone on prostaglandin metabolite concentrations, myometrial contractility and response to oxytocics in the second trimester of pregnancy and to elucidate the mechanism of progesterone myometrial suppression and the physiological control of parturition.

Subjects and methods

A double blind, placebo controlled study was performed including 20 primigravidae at 16–18 weeks gestation scheduled for pregnancy termination by extra-amniotic injection of prostaglandin within the terms of the Abortion Act 1967. All patients gave informed consent and local ethics committee support for the study was obtained. Following entry into the trial, gestation was determined by clinical and ultrasonic examination. Subjects were treated orally with either mifepristone, 600 mg, or an identical placebo 24 h before the planned termination. Randomization was carried out by Roussel Laboratories using a predetermined code balanced within groups of ten. The only exclusion criteria were the patients parity and eligibility for mifepristone treatment. Before treatment a peripheral venous blood sample was taken for haematological (Hb and blood group), and hormonal (ß-hCG and prostaglandin metabolites) analyses (pre-treatment sample). The PGEM and PGFM levels were repeated 24 h later when the subject was admitted (post-treatment sample), and again 6 h after instillation of prostaglandin into the uterus (post-PG sample).

On admission to hospital an intravenous infusion of dextrose-saline was started and Gaeltec pressure tip catheter was passed transcervically. This was secured by a 14G Foley catheter with a 5 ml balloon which was passed alongside the pressure catheter to retain it in the correct position. After a 20-min recording of 'baseline intrauterine pressure, a 30 min metered infusion of oxytocin, 100 mu/min (oxytocin phase) was started, followed after a 30-min interval by a 30-min infusion of PGE_2, 2μg/ml (PG phase); in order to exclude any bias, the order of the oxytocin prostaglandin was alternated. In the first 10 women an intravenous dose of ergometrine, 0·25 mg, was given after the infusions and the uterine pressures were recorded for a further 30 min. PGE_2, 1·5 mg in 10 ml of 6% Tylose gel, was then injected into the extra-amniotic space via the Foley catheter and uterine activity recorded for a further 60 min period before removal of the catheters. Intrauterine pressure was measured continuously throughout the infusions and rest periods, and recorded directly onto computer discs: 10-min epochs were later analyzed using a program quantifying uterine activity in activity units (Hon & Paul 1973; M. Selinger *et al.* 1987).

Six hours after the PGE_2 instillation, a constant infusion of oxytocin, 100 mu/ml, was started and maintained until abortion. Subsequent management was as described previously by Hill & MacKenzie (1989). The induction-abortion interval (IAI) was defined as the time from prostaglandin injection into the uterus to expulsion of the products of conception.

Three-way analysis of variance (treatments, time (10-min epochs), and treatment with time) was used to assess differences between the mifepristone and control groups for each phase of uterine activity (baseline, oxytocin, prostaglandin, ergometrine and prostaglandin gel).

PGFM (13, 14-dihydro-15-oxo-prostaglandin $PGF_{2\alpha}$) was estimated by radioimmunoassay as described previously (Mitchell *et al.* 1978), and radioimmunoassay of PGEM (13, 14-dihydro-15-oxo-PGE_2) was measured after conversion to its stable bicyclo derivative (Demers *et al.* 1983).

Results

Patients details relating to age, height, weight, gestational age and ß-hCG concentration are shown in Table 1. No drug reactions or side-effects were recorded after mifepristone treatment and no patient had vaginal bleeding or uterine pain during the interval before prostaglandin treatment. During the pressure studies no patient had vaginal bleeding or expelled the transducer.

The effects of the various oxytocic agents on uterine activity are shown in Figure 1. The baseline uterine activity in the patients treated with mifepristone was significantly greater than the activity in the placebo group ($P \leq 0{\cdot}0001$, $F = 18{\cdot}5$). There was no significant difference in the uterine activity during the oxytocin infusion between the two groups ($P \leq 0{\cdot}33$, $F = 0{\cdot}95$). The uterine activity during the prostaglandin infusion in the mifepristone group was statis-

Table 1. Mean (SD) characteristics of patients with mifepristone or placebo

	Mifepristone (n = 10)		Placebo (n = 10)	
Age (years)	22·4	(3·0)	21·0	(2·1)
Height (cm)	163	(2·6)	161	(3·1)
Weight (kg)	58·4	(8·9)	57·9	(9·6)
Gestation (weeks)	16·6	(0·78)	16·9	(0·83)
(ß-hCG (IU/1)	12 605	(4 949)	14 407	(7 563)

tically significantly greater than the activity in the placebo group ($P \leq 0{\cdot}002$, F = 10·5). The infusion order did not influence the uterine responses. The mean uterine activity after extra-amniotic prostaglandin injection in the mifepristone group was significantly greater than the activity in the placebo group ($P \leq 0{\cdot}002$, F = 9·84). Similarly in the ten women treated with ergometrine, the uterine activity after ergometrine injection was significantly greater in the mifepristone group than in the placebo group ($P \leq 0{\cdot}002$, F = 11·0) (Fig. 2).

The plasma concentrations of PGEM and PGFM did not differ significantly between the two treatment groups at any of the time intervals studied after treatment (Fig. 3). There were no significant changes in the PGEM and PGFM concentrations before extra-amniotic PGE_2 prostaglandin injection in either the mifepristone or placebo group. However, in both groups the PGEM and PGFM concentrations after the therapeutic injection of PGE_2 were significantly higher than the pre-treatment concentrations ($P \leq 0{\cdot}001$, Mann–Whitney U-test).

The mean (SD) induction-abortion interval (IAI) in the subjects treated with mifepristone was 512 (321) min which was significantly shorter than the mean (SD) IAI of 1128 (606) min in the control group ($P \leq 0{\cdot}02$, Mann–Whitney U-test). Fifty percent and 90% of the mifepristone patients aborted within eight and 12 hours of prostaglandin instillation in the uterus, compared with 10% and 40% respectively in the control group (Fig. 4). All patients aborted without complication and were discharged from hospital within 48 hours of admission There was however no association between the induction abortion interval and prostaglandin metabolite concentrations.

Gastrointestinal side-effects were the only side-effects encountered, with 25% and 8% of patients respectively having vomiting or diarrhoea on at least one occasion. Analgesia was given to 17 (85%) patients during the contractile phase and four (16%) required a surgical evacuation of the uterus for immediate incomplete

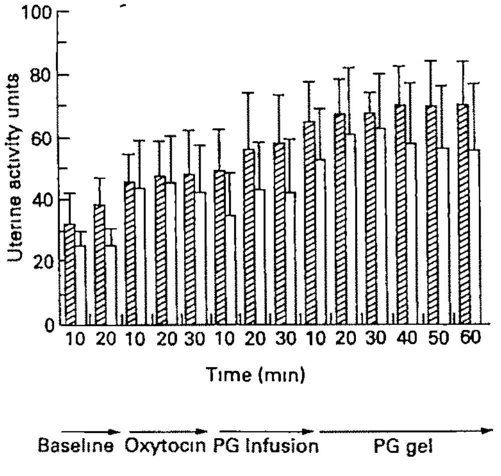

Fig. 1. Mean (SD) uterine activity measured in uterine activity units in the mifepristone (hatched, n = 10) and placebo (plain, n = 10) groups for each 10 min epoch during the baseline, oxytocin and prostaglandin phases of the study.

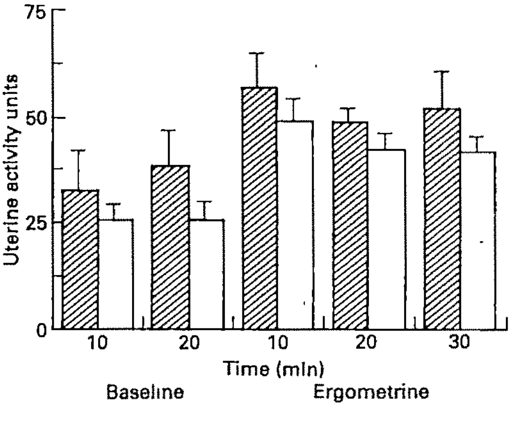

Fig. 2. Mean (SD) uterine activity measured in uterine activity units in the mifepristone (hatched, n = 5) and placebo (plain, n = 5) groups for each 10 min epoch during the baseline and ergometrine phases of the study.

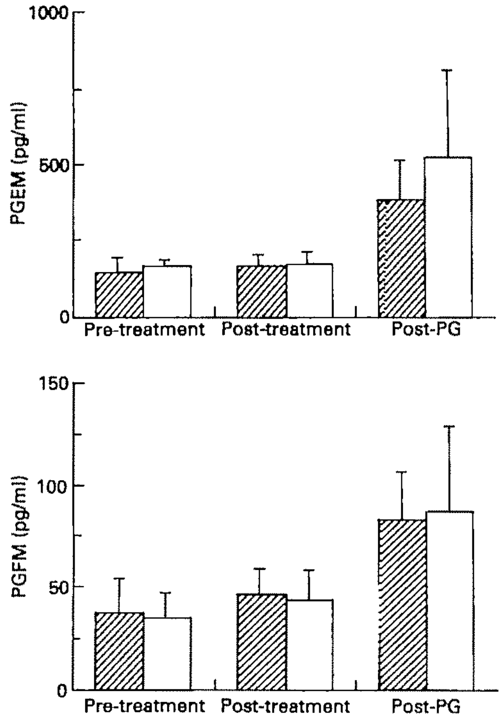

Fig. 3. Mean (SD) PGEM and PFGM concentrations during study in women treated with mifepristone (hatched, *n* = 10) and placebo (plain, *n* = 10)

expulsion of the pregnancy. There was no significant differences in these indices between the two treatment groups.

Discussion

Mifepristone has been shown to stimulate spontaneous uterine activity in primates (Haluska *et al.* 1987) and in the first trimester of human pregnancy (Bygdeman & Swahn 1985; Swahn & Bygdeman 1988). Our study was designed to measure the effect of mifepristone on PGEM and PGFM concentrations, and on myometrial activity and sensitivity to prostaglandin, oxytocin and ergometrine in the second trimester.

The quantification of myometrial activity by intrauterine pressure recordings analyzed by computer, thus eliminating any error due to free-hand interpretation, demonstrates that treatment with mifepristone results in an increase in baseline uterine activity and increased sensitivity to PGE$_2$ and ergometrine during the second trimester of pregnancy; a similar increase in baseline uterine activity has been reported in the second trimester after progesterone withdrawal with epostane, a 3-β hydroxysteroid dehydrogenase enzyme antagonist (Selinger *et al.* 1987). The lack of enhanced sensitivity to oxytocin in this study was also found when epostane was used in the first (Webster *et al.* 1985) and second trimesters of pregnancy (Selinger *et al.* 1987). This might be due to the very low levels of oxytocin receptors found in the uterus at this stage of pregnancy (Fuchs *et al.* 1984). The increased spontaneous activity and sensitivity of the myometrium after mifepristone treatment probably results from progesterone withdrawal at a cellular level after blockage of the progesterone receptors (Baulieu 1985). It may in part also be due to down regulation of the progesterone receptors by mifepristone, since progesterone receptor concentrations have been shown to decrease in the decidua after mifepristone treatment (Hill *et al.* 1990a).

The exact mechanism by which progesterone controls myometrial activity is controversial. Progesterone is known to inhibit gap junction formation in the myometrium (Garfield & Hayashi 1981; Saito *et al.* 1985), and gap junctions are thought to be essential for efficient electrical coupling between the myometrial cells, and therefore coordinated uterine activity (Garfield 1984). The inhibitory effect on the replenishment of cytosolic oestrogen receptors (Fuchs & Fuchs 1984) and the stimulatory effect of the hormone on the formation of β-adrenoreceptors in the myometrium (Roberts *et al.* 1981) may also be of importance. Progesterone may also act by stabilizing lysosomal membranes which are thought to be important in endogenous prostaglandin production (Gustavii 1972). Therefore withdrawal of progesterone by mifepristone may stimulate endogenous prosta-

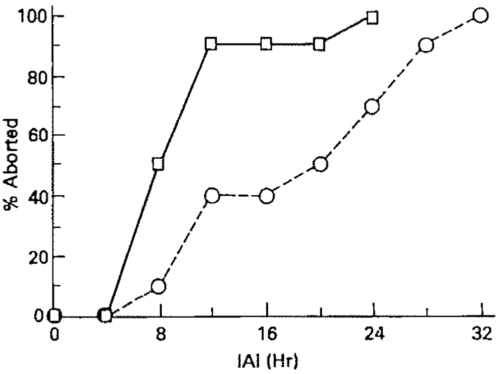

Fig. 4. Induction to abortion interval (IAI) in women treated with mifepristone (—□—) or placebo (--○--).

glandin production and intrauterine activity. The drug has been found to increase prostaglandin production *in vitro* from the glandular cells in early human decidua (Smith & Kelly 1987) and from the endometrial stromal cells during the menstrual cycle (Kelly *et al.* 1986). We have not found a similar response *in vivo* but our failure to demonstrate any significant increase could have been because the time interval between drug administration and metabolite measurement was too short. In primates no increase in prostaglandin metabolite concentrations can be demonstrated until 48 h after mifepristone treatment (Haluska *et al.* 1987), but we have been unable to demonstrate an increase 48 h after treatment during the first trimester (Hill *et al.* 1990b). Mifepristone may therefore act by increasing local production of prostaglandin within the uterus without it being reflected in the concentration of prostaglandin metabolite in the peripheral circulation, or as the drug has been shown to inhibit the metabolism of prostaglandin by decidual cells *in vitro* (Smith & Kelly 1987), it is possible that there is an increase in the production of primary prostaglandins in the uterus without a corresponding increase in production of the metabolites. Finally mifepristone may act by increasing the myometrial response to the prostaglandins already synthesized and not by increasing basal production.

The dramatic reduction in the induction-abortion interval by more than half from 1128 (606) min to 512 (321) min in the mifepristone group was of considerable benefit to patients in reducing the need for or duration of oxytocin infusion, together with the potential of reduced inpatient stay. This reduction, similarly obtained with progesterone synthesis suppression, was achieved with a small dose of PGE$_2$ (1·5 mg), which is also an advantage as the gastrointestinal side-effects of prostaglandin are dose related (MacKenzie & Embrey 1976). Day-case prostaglandin termination of mid-trimester pregnancy thus becomes a realistic possibility after mifepristone priming of the uterus.

These data add further evidence for the hypothesis that the pregnant uterus is an organ suppressed by progesterone, and when this is withdrawn it becomes more contractile and sensitive to exogenous oxytocics. Enhanced results have already been reported for mid-trimester termination of pregnancy (Urquhart & Templeton 1987), and intrauterine fetal death (Cabrol *et al.* 1985; Padayachi *et al.* 1988). The possibility of another agent to help improve the outcome of induced term labour becoming available in a few years may now be realised.

Acknowledgments

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The effect of caput succedaneum on oxygen saturation measurements

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Summary. Advances in oximetry have allowed the obstetrician to measure oxygen saturation in the fetus with non-invasive transcutaneous techniques. The influence of caput succedaneum formation on the oxygen saturation results obtained with a pulse oximeter was studied in 30 newborn infants. Caput was associated with a reduced oxygen saturation reading (mean reduction of 15%; $P<0{\cdot}001$). This effect is partly due to a true drop in local tissue oxygenation but is exacerbated by a systematic error intrinsic to the physics of spectrophotometry. If continuous intrapartum oximetry is ever to become a part of routine obstetric monitoring then probes that pass through the cervix beyond the caput of the presenting part will be required if erroneously low readings are to be avoided.

With the advent of reflectance pulse oximetry it has become possible to measure fetal oxygen saturation (SaO_2) non-invasively through ruptured and intact membranes (Peat *et al.*, 1988; Johnson & Lilford, 1988; Johnson & Johnson, 1989; Gardosi *et al.*, 1989; Johnson *et al.*, 1989a, 1989b and 1990).

The physical principles of oximetry are simple but their understanding is vital before the limitations of oximetry can be appreciated. Pulse oximeters measure the light absorbed by the pulsatile vascular bed. They commonly consist of light emitting diodes transmitting 700–1000 pulses/s and the light transmitted through the skin is measured by a single adjacent photosensitive cell. If the detected light intensity is low then the oximeter automatically increases the power to the light sources. Deoxygenated and oxygenated haemoglobin have different light absorption characteristics; deoxygenated haemoglobin absorbs more red light than oxygenated haemoglobin but at the infra-red range of the spectrum this difference is non-existent or even reversed. Therefore the ratio of absorbed infra-red and red light is related to the oxygen content of haemoglobin. Detected light that has been transmitted through the skin can be considered to consist of two components; a pulsating or alternating component superimposed on top of an adynamic or direct component. The alternating component represents only the light that has been absorbed by pulsating arterial blood whilst the adynamic component represents light absorption by venous blood, skin and tissue (Figure 1; Tremper & Barker, 1989; Wukitsch, 1987; Taylor & Whitwam 1986). Conventional oximeters transmit light through tissues (transmission oximetry) but the use of wide angle photosensitive cells means transilluminated (backscattered) light from an adjacent light source can be detected (reflectance oximetry). Probes can therefore be applied to flat surfaces and this represents the potential to be an

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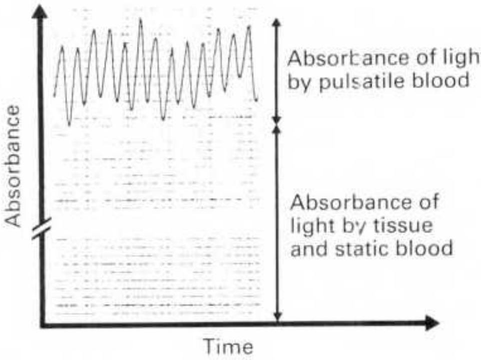
Absorbance of light by pulsatile blood
Absorbance
Absorbance of light by tissue and static blood
Time

Fig. 1. The absorbance of infra-red light that has passed through body tissue as detected by an oximeter photodetector. The pulsatile component of the absorption spectrum (the plethysmograph) is produced by light absorbed by pulsatile blood. The static component represents light absorption by tissue, venous blood and other body fluids.

exciting new method of monitoring the intrapartum fetus. Pulse oximeters are cheap, robust, accurate (Yelderman & New 1983) and respond rapidly to changes in arteriolar oxygen content but if caput succedaneum formation affects transcutaneous oxygen saturation readings then this innovation will be limited as a method of continuous fetal monitoring.

We therefore investigated the effect of caput on pulse oximetry. (1) We examined babies born with caput and we also examined babies with no caput to exclude a possible difference due to measurements taken from different parts of the scalp. (2) To determine whether reflectance pulse oximetry was specifically affected by caput or by a general increase in extracellular fluid we studied a newborn infant with generalized oedema. (3) By studying the light absorption characteristics of fetal plasma we determined whether the effect of caput and oedema on arterial oxygen saturation was real or a possible error in the oximeter's interpretation of the data.

Subjects and methods

The effect of caput on pulse oximetry

A reflectance pulse oximeter (Criticare 502; Severinghaus & Naifeh, 1987; Spectramed of Coventry and Simonsen & Weel Ltd of Sidcup) was adapted to measure oxygen saturation over a flat tissue surface by uniting the light emitting diodes and a wide angle light sensitive diode in the same plane (Fig. 2). The infra-red signal was displayed in a plethysmographic form on a chart recorder to confirm the arterial origin of the signal for each reading.

A total of 30 Caucasian infants was selected according to their availability and examined at birth. The first group consisted of 20 babies who had obvious caput formation following delivery (++ or +++caput) and the second group included ten babies who were born by elective caesarean section and consequently were free of caput. Caput was graded subjectively (0-no caput; +mobile; ++fixed but underlying sutures palpable; +++sutures not palpable beneath the caput). As soon as the baby was born it was wrapped in a towel and its head was wiped clean. Transcutaneous oxygen saturation was measured with the modified probe in the foot and two sites on the scalp according to one of the following sequences selected at random (i) apex of caput (occiput if no caput), temporal

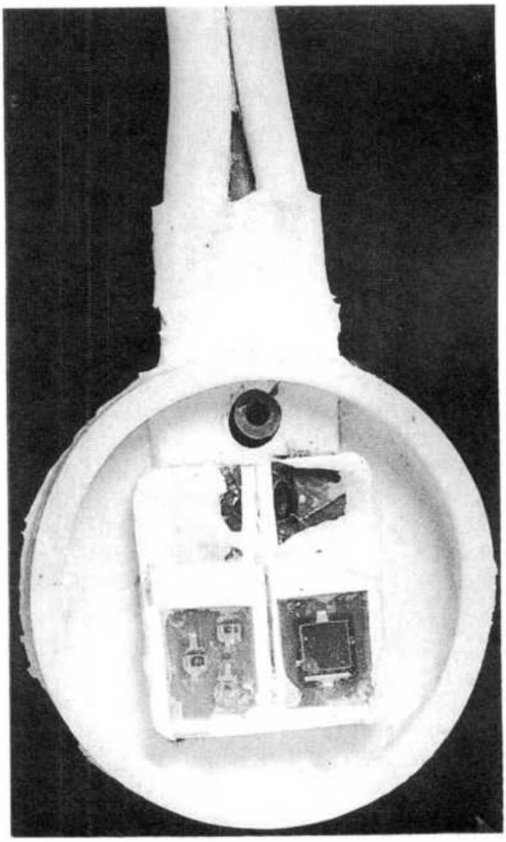

Fig. 2. Fetal oximetry probe housed in a suction cup.

region, and again the apex of the caput or (ii) temporal region, caput, temporal region. These readings were considered to be of good quality if (i) the oxygen saturation of the first reading was within 10% of the third reading, (ii) if the pulse rate recorded by the oximeter was within 10 beats/min of the neonatal heart rate and (iii) a representative sinusoidal plethysmograph was obtained (Fig. 1). Three infants were excluded because it was impossible to obtain a reproducible sinusoidal pulse wave pattern from the caput. Measurements were repeated every 30 min until the caput resolved or the oxygen saturation of the caput was similar to that over the temporal regions. The oxygen saturation over the caput was compared with that over the temporal region in both groups by a two-tailed Student's paired *t*-test. The quality of the plethysmograph was assessed subjectively by an observer who was unaware of the origin of the traces. A top score of five was awarded for a perfect sinusoidal graph and the plethysmograph scores from the foot and scalp were analysed by Wilcoxon matched-pair signed-ranks test.

The effect of generalized oedema on pulse oximetry

In an attempt to explain the observed reduction in oximetry readings taken from areas of caput, the effect of oedema on reflectance pulse oximetry was investigated. Reflectance and transmission pulse oximetry and arterial gas analysis (Radiometer ABL 300, Copenhagen) was performed in an oedematous newborn infant who had developed respiratory distress syndrome following meconium aspiration.

The effect of caput on the physics of pulse oximetry

To explain why caput and oedema affect reflectance oximetry, the relative absorption of red and infra-red light by extracellular fluid was estimated. The absorption spectra of fetal plasma was measured in triplicate with a CE 303 Grating spectrophotometer (Cecil Instruments, Cambridge) at wavelength increments of 10 nm. The effect of extracellular fluid on reflectance oximetry was mimicked by placing light filters (Projectafilm Letraset colour correction filters) with an absorption spectrum similar to extracellular fluid between the probe and skin.

Results

The effect of caput on pulse oximetry

The oxygen saturation recorded over the caput was lower than that recorded over the temporal region in all but one of the newborn babies (Fig. 3). The mean oxygen saturation over the caput in the newborn was 69% (SD 13%) compared with 84% (SD 6%) over the temporal region. This difference is statistically significant; $t = 5\cdot3$; $P<0\cdot001$; paired Student's *t*-test. There was no difference in the oxygen saturation recorded over the occiput (mean = 83%) and temporal region (mean = 81%) in babies with

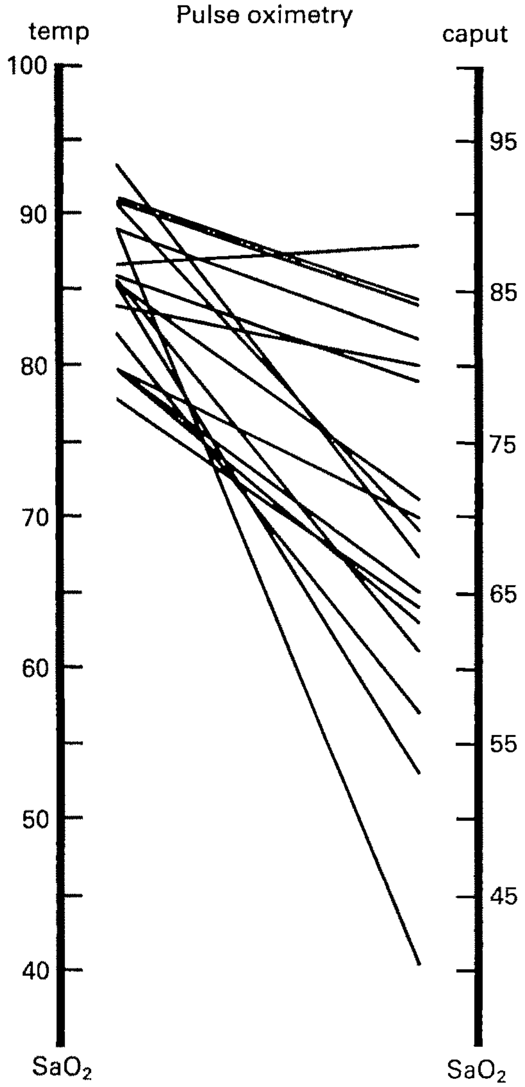

Fig. 3. The mean oxygen saturation recorded at birth over the caput and over the temporal region; $t = 5.3$, $P<0\cdot001$.

no caput (those born by elective caesarean section) ($P = 0{\cdot}8$). In babies where caput was present the differences between the oxygen saturation recorded over the temporal and occipital regions decreased with time. By 6 h the difference between oxygen saturation recorded over the occiput and temporal regions was less than 3% in all babies.

The quality of the continuous oxygen saturation plethysmograph recorded from scalp of babies born with caput was inferior to readings obtained from the foot. The median score award for plethysmograph quality obtained from the caput was 2 and only two traces scored ≥4. The median score from the foot was 4 and eight readings scored ≥4 ($P<0{\cdot}001$; Wilcoxon matched-pair signed ranks test). The median score for plethysmograph quality from the temporal region was 3. The median plethysmograph score for all babies born by elective caesarean section (ie without caput) was 4 but plethysmograph quality was similar from the occiput and temporal region.

The effect of oedema on pulse oximetry

In the baby with generalized oedema the oxygen saturation recorded by transcutaneous reflectance pulse oximetry was consistently lower than the transmission pulse oximetry probe and arterial blood gas analysis. Over a 30-min period the apparent oxygen saturation recorded from the baby with generalized oedema, as measured by reflectance pulse oximetry, ranged from 70–90% (median 75%) compared with a median reading of 93% (range 90–96%) for the transmission pulse oximetry probe and 92·8% for arterial blood gas analysis. This difference persisted until the baby's oedema resolved.

The effect of oedema on the physics of pulse oximetry

Fetal plasma absorbs more visible-red than infra-red light (Fig. 4). When photographic filters with absorption characteristics similar to plasma were placed between the reflectance probe and skin the oximetry reading fell.

Discussion

Elegant laser Doppler studies have shown that blood flow is independent of caput formation (Smits & Aarnoudse 1984). As oximetry is designed to display pulsatile oxygen saturation, readings should represent the oxygen saturation of arteriolar blood and are theoretically independent of venous stasis or local tissue oedema. It might therefore be expected that oximetry will not be influenced by caput. However, despite these theoretical considerations, our findings show that oxygen saturation readings from the caput are consistently lower than in less oedematous regions of the newborn's scalp, and this is confirmed in a baby with generalized oedema.

There are two explanations; either caput affects the true or the apparent oxygen saturation. We think that both of these factors may be at work.

Caput may affect the apparent arterial oxygen saturation because of its association with oedema and venous congestion and some of the arterial pulsations may be transmitted to the deoxygenated extracellular fluid and venous blood. The oximeter interprets all pulsations as arteriolar and therefore incorporates the pulsatile venous component into the oxygen saturation equation. An analogous phenomenon has also been observed in the finger (Kim *et al.*, 1985). However, this would not explain why the reflectance oximetry results in the baby with generalized oedema were lower than expected. Oedema is characterized by an increase in extracellular fluid. This acts as an interface between the probe and the vascular bed absorbing more red than infra-red light. This preferential absorption of red light can be reproduced by placing a light filter between the skin and probe. Both caput and a filter absorbing red light decrease the value of oximetry readings. In other words, reflectance oximetry is affected by an accumulation of extra cellular fluid which can

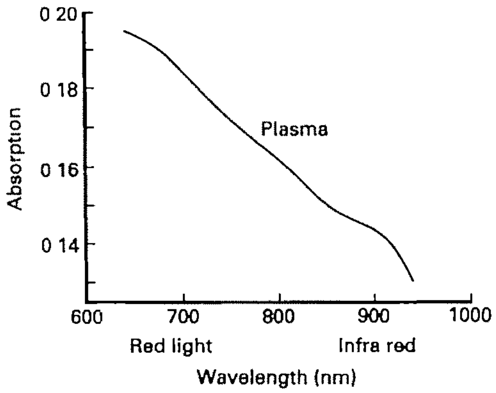

Fig. 4. The absorption spectrum of fetal plasma.

be reproduced by placing a filter that mimics the absorption spectrum of plasma between the probe and a subject's skin.

This error, which is intrinsic to the physics of reflectance spectrophotometry and the empirical nature of oximeters, would cause lower arterial oxygen saturation readings. However, it is also possible that caput is associated with a true reduction in arterial oxygen saturation. Although caput is said not to affect local blood flow it is probably associated with a reduction in the local partial pressure of oxygen (Wallenburg *et al.*, 1983, O'Connor & Hytten, 1979) and, despite the theoretical advantage of measuring oxygen saturation during systole, back pressure and a low local oxygen tension (PaO_2) may prevent completely arterialized blood entering the skin even at the start of the cardiac cycle. It may be inferred from the oxygen dissociation curve that if caput formation is associated with a reduced PaO_2, oxygen saturation recorded over the oedematous tissue of caput would be considerably lower than that of the surrounding scalp.

A possible explanation for the larger range of results obtained from oedematous areas of the newborn may be inferred by analysis of the Beer-Lambert law (The Beer-Lambert law states that light transmission decreases exponentially as the distance it travels increases and as the concentration of the light absorbing molecules it passes through increase). Local tissue oedema will increase the mean distance photons have to travel before being absorbed by haemoglobin.

Reflectance oximetry requires light to be reflected (bounced) and any increase in distance of the vascular bed from the source will double the extra distance light has to travel in order to be sensed by the reflectance probe. As light absorption is an exponential function of distance, loss and scatter of photons will increase with the oedema of caput and this will have a significant effect on the accuracy of a reflectance pulse oximeter. This same pheonomenon of tissue oedema influencing oximetry was also observed in the oedematous newborn who presented with meconium aspiration. Loss of photons due to greater distance travelled in oedematous tissue is supported by our observation that it was considerably more difficult to obtain a sinusoidal pattern which was free from interference. Experiments on adult volunteers has shown that the performance of an oximeter is affected by obstructing venous return and this could further explain the wider range of results in the presence of caput (Wilkins *et al.*, 1989).

The development of wide-angle light-sensitive probes, permitting reflectance oximetry, has opened the door to a new form of non-invasive transcutaneous fetal monitoring. However, obstetricians should be cautious of readings obtained from a presenting part that develops oedema. The oxygen saturation of caput as recorded by the oximeter will be lower than the oxygen saturation of the fetus as a whole.

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The perurethral technique for ultrasound directed follicle aspiration in an in-vitro fertilization and embryo transfer programme: a report of 636 patient cycles

MICHAEL BOOKER, JOHN PARSONS

Summary. The data from 636 patient cycles from an outpatient-based in-vitro fertilization and embryo transfer programme are presented. Between 1984 and 1988, 545 women (86%) underwent ultrasound directed follicle aspiration (UDFA) exclusively by the perurethral route. The mean follicle aspiration rate was 93%, and the mean number of oocytes per procedure was 5·8. The complication rate was 6%, but none was major. From July 1985 the clinical pregnancy rate per UDFA was 17% and per embryo transfer 21%. The perurethral approach was used in combination with another UDFA route in 91 women (14%) but the need to change route decreased with increasing operator experience. Perurethral UDFA is an efficient and safe method for harvesting oocytes.

Ultrasound directed follicle aspiration (UDFA) has now largely replaced laparoscopic oocyte retrieval, initially practised by Steptoe *et al.* (1980) for in-vitro fertilization and embryo transfer (IVF-ET), because it is simpler and can be performed on an outpatient basis without the need for general anaesthesia.

UDFA by the transabdominal transvesical route was first described by Lenz *et al.* (1981), and subsequently reported by Lenz & Lauritsen (1982), Wikland *et al.* (1983), and Riddle *et al.* (1987). Ovaries lying superior to the uterus may be more easily reached by direct transabdominal puncture without going through the bladder. Transvaginal UDFA under transabdominal ultrasound guidance was first described by Gleicher *et al.* (1983). Dellenbach *et al.* (1985) described the transvaginal transvesical approach. The perurethral technique for UDFA was developed from these approaches by Parsons *et al.* (1985). They noted that the needle was seen more clearly than with the transabdominal transvesical approach because it was at 90° to the ultrasound beam, rather than crossing it obliquely. Subsequently Wikland *et al.* (1985) and Feichtinger and Kemeter (1986) described the use of the vaginal ultrasound transducer when performing UDFA by the transvaginal route. We describe our experience of the perurethral technique between 1984 and 1988.

Subjects and methods

All the women included in the study were rubella immune with normal thyroid function, normal serum prolactin levels, and normal cervical cytology, and had had a laparoscopy as part of their infertility investigations. Dense pelvic adhesions were not regarded as a contra-indica-

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Table 1. Indications for IVF-ET using perurethral ultrasound directed follicle aspiration (UDFA)

Indication	Perurethral route only *n*	(%)	Perurethral combined with other routes *n*	(%)
Tubal damage	424	(78)	73	(80)
Endometriosis	10	(2)	4	(5)
Unexplained infertility	38	(7)	2	(2)
Oligospermia	9	(1·5)		
Vasa aplasia	4	(0·5)	2	(2)
Other male factor	6	(1)	2	(2)
Immunological	4	(0·5)	1	(1)
Premature menopause	4	(0·5)		
Tubal damage + male factor	20	(4)	1	(1)
Tubal damage + endometriosis	16	(3)	2	(2)
Other combined	10	(2)	4	(5)
Total	545		91	

tion to UDFA. Of the 545 women who had UDFA exclusively by the perurethral route, six were treated in 1984, 181 in 1985, 280 in 1986, 63 in 1987, and 15 in 1988, and of the 91 women who had UDFA by the perurethral route in combination with another route, two were treated in 1984, 34 in 1985, 31 in 1986, 16 in 1987, and eight in 1988. The mean ages (SD) in the two groups were 32·4 years (4·1) and 33·6 years (3·7) respectively. The indications for IVF-ET are summarized in Table 1.

Ovarian stimulation

Of the 636 women, 599 (94%) were treated with an overlap regimen of clomiphene citrate (Clomid; Merrell, Hounslow, UK) 100 mg daily from day 2 to day 6, with human menopausal gonadotrophin (hMG) (Pergonal; Serono Laboratories, Welwyn Garden City, UK) 1–6 ampoules daily, starting on day 2 or day 4 of the cycle, the dose and day of starting depending on the woman's age, menstrual cycle length, and previous response to ovarian stimulation. Sixteen women (3%) received pure follicle stimulating hormone (FSH) (Metrodin; Serono Laboratories, Welwyn Garden City, UK) instead of, or in addition to, hMG in a similar overlap regimen. The remaining 21 women (3%) were down-regulated with the gonadotrophin—releasing hormone (GnRH) analogue, buserelin, (Suprefact; Hoechst, Hounslow, UK), before beginning stimulation with either hMG, FSH, or both.

All women had an ultrasound scan on day 2 of the cycle to assess ovarian morphology. Subsequent scans were performed daily after the start of hMG or FSH. Up to the last quarter of 1986, all scans were performed abdominally using a mechanical sector scanner (DRF 100; Diasonics, Bedford, UK) with an abdominal 3·5 MHz transducer. Thereafter, following a transition period, all scans were performed vaginally using a mechanical sector scanner (Bruel and Kjaer, Copenhagen, Denmark) with a 7 MHz vaginal transducer. Occasional women continued to be scanned abdominally.

The response to ovarian stimulation was monitored by ultrasound to determine the size and number of developing follicles. From mid-1986 this was complemented by a daily serum oestradiol assay. When the leading follicle had reached a mean diameter of 17 mm, or when there were two follicles of 16 mm mean diameter, human chorionic gonadotrophin (Profasi; Serono Laboratories, UK) 5000 IU, (10 000 IU for women who had received GnRH), was administered and UDFA performed 34–36 h later. The additional criterion of a satisfactory rise in the serum oestradiol level was added after mid-1986.

Ultrasound directed follicle aspiration (UDFA)

Lorazepam (Ativan; Wyeth, Maidenhead, UK) 1 mg orally was given the night before, and again 2 h before the procedure. Women were asked to fast overnight, and micturate immediately

Table 2. Routes used in addition to perurethral route for follicle aspiration in 91 woman

	Total no		Follicles		
				No. aspirated	
Additional route	*n*	(%)	Total no.	*n*	(%)
Transabdominal transvesical	19	(21)	166	142	(86)
Transabdominal (direct)	18	(20)	203	178	(88)
Transvaginal (direct)	51	(56)	719	574	(80)
Combination of more than two routes	3	(3)	36	31	(86)
Total	91		1124	925	(82)

before the UDFA to ensure an empty bladder. Their partners were asked to provide a semen sample before or after the procedure, and were encouraged to attend. Incremental doses of 25 mg pethidine (Roche Products Ltd., Welwyn Garden City, UK) and 2·5 mg diazepam (Diazemuls; Kabivitrum Ltd., Uxbridge, UK) were administered intravenously before and during the procedure to provide analgesia and sedation. When necessary, the anti-emetic, metoclopramide 10 mg (Maxalon; Beecham Research Laboratories, Brentford, UK), was added. All UDFA procedures were performed in a minor operating theatre with an integral laboratory.

A 27·2 cm long double-channel needle was used for the procedure (Casmed, Cheam, UK). The outer disposable channel is sharp-ended and has an outer diameter of 1·7 mm. The inner reusable channel is blunt-ended and has an inner diameter of 0·93 mm. The latter is connected by PTFE tubing to a 15 ml test tube (Falcon; Becton and Dickinson, London, UK), to which suction is applied from a foot operated pump (Craft; Rocket, Watford, UK). When the needle is assembled, the two concentric channels are joined by a Luer lock fitting. When the needle is inside a follicle and suction applied, the follicular contents are aspirated into the test tube. The aspirate is examined immediately in the adjacent laboratory, and if an oocyte is not found, the follicle is flushed with culture medium (EBS) (Earle's balanced salt solution; Gibco, Paisley, Scotland) by connecting a syringe of medium to the outer channel of the needle via a length of PTFE tubing, and injecting sufficient medium to fill the follicle. Repeated flushing of the follicle is continued until the oocyte is recovered, or until the flushings cease to contain granulosa cells.

All women had UDFA by the perurethral route, and for 91 women (14%) an additional route was used to maximize the number of follicles aspirated (Table 2). For each procedure we recorded the number of follicles on the day of UDFA, the number of follicles aspirated and the number of oocytes retrieved, and if there were any difficulties or complications. The cycle outcome was also recorded. Pain and analgesia requirement, and the length of the procedure were recorded in a subgroup of women in 1987.

Perurethral UDFA

The woman is placed in the lithotomy position with the operator standing on her right. After performing vulval toilet with a solution of cetrimide and chlorhexidine (Savlodil; ICI, Macclesfield, UK), followed by EBS, the needle tip is placed in the side-hole of a 14 Ch Foley catheter, and the two are inserted into the bladder via the urethra. The bladder is then filled with Hartmann's solution via a giving set, the catheter balloon inflated, and the needle tip disengaged from the catheter. The needle tip is then advanced with a single thrusting motion through the posterior wall of the bladder, and into the ovary under ultrasound guidance. Follicles are aspirated and flushed until all available follicles have been emptied. At the end of the procedure the needle is withdrawn, the bladder emptied, and the catheter removed. The woman is allowed home after 1 to 2 h. If haematuria is noted during the UDFA procedure, she is encouraged to drink and void urine before going home.

Additional UDFA routes

For the transabdominal transvesical route, the procedure is the same except that the needle is inserted through the anaesthetized (1% lignocaine (Antigen Ltd, Roscrea, Ireland)) area of the abdominal wall and into the bladder, before passage through the posterior wall of the bladder and into the ovary. For the transvaginal route using the transvaginal ultrasound transducer, a needle guide is attached to the transducer before inserting it into the vagina. A follicle is aligned on the ultrasound screen, and the needle advanced with a single thrusting movement through the vagina and into the target follicle. Follicles can be aspirated and flushed in turn, as with the other UDFA approaches.

IVF-ET procedure

Oocytes were transferred into 1 ml EBS supplemented with 10% (v/v) heat-inactivated woman's serum. Insemination was performed 4–6 h after UDFA, and examination for the presence of two pronuclei 17–19 h later. Embryos were transferred 48 h after UDFA using a Bourn-Wallace catheter (Wallace Ltd, Colchester, UK). The number transferred was restricted to four from mid-1986, and to three from the beginning of 1987.

Cycle outcome

It menses had not returned within 16 days of the UDFA, serum β-hCG was assayed, and a level of >50 IU/l was taken as indicative of pregnancy. Pregnancy definitions were taken as those described by Jones *et al.* (1983). Preclinical pregnancy was defined as a pregnancy not proceeding beyond 28 days after oocyte collection.

Results

In those women where only the perurethral route was used, the mean number of follicles was 10·4 (SD 4·8), and the mean number of follicles aspirated 9·5 (SD 4·5). The mean follicle aspiration rate was 93%, but varied from 82% in 1984 to 95% in 1986, the year in which we did the most perurethral procedures. In 175 cycles (32%) some of the follicles were not aspirated; Table 3 gives details of the reasons. In 85 of these (49%) this was because the follicles were small and in 38 (22%) because of difficulty reaching all the follicles. The mean number of oocytes per collection and per follicle were 5·8 (SD 3·3) and 0·62 (SD 0·23), respectively.

When another route was employed in addition to the perurethral route, the choice of route is given in Table 2. Of these 91 patient cycles, the reasons for changing route were difficult access (41%), ovary in the cul-de-sac (20%), high ovary (9%), subcutaneous ovary (2%), mobile ovary (1%), difficulty in maintaining a full bladder (1%), and a combination of reasons (1%). No reason was given in 25%. The frequency of need to change route fell from 25% in the last quarter of 1984 to 5% in the last quarter of 1985, and then rose to 35% in 1988. When a combination of routes was necessary, 82% of follicles were successfully aspirated.

The need for analgesia and an assessment of pain experienced were assessed in a subgroup of 23 women in 1987. The mean pethidine requirement was 107 mg (SD 33), and the pain categories were none (1 woman), minimal (2 women), occasional sharp (17 women), and frequent sharp (3 women). No woman experienced constant or unbearable pain, and all said they would undergo the procedure again if necessary. The mean time taken for the UDFA procedure was 42 min (SD 13).

In the 545 patient cycles where the perurethral route was used exclusively, 34 women experienced complications (6%). Extravasation of urine was the most frequent complication (13 women), but this did not lead to any adverse clinical sequelae. Seven women experienced haematuria, four of them needed catheterization and bladder irrigation; in all seven women the bleeding resolved spontaneously. One woman had extravasation of urine and haematuria. In three women where a pelvic vessel was inadvertently punctured, the needle was immediately withdrawn, and there were no further problems. In nine women the procedure was complicated by opioid depression, and in one by vomiting.

Tables 4 and 5 summarize the embryo transfer and pregnancy data. We had to wait 9 months to achieve our first pregnancy following perurethral UDFA, but thereafter the pregnancy rate for women who had at least three embryos transferred was 27%. The pregnancy outcome data are summarized in Table 6. There were three pregnancies involving perinatal loss associated with preterm labour. The twin and triplet pregnancy rates expressed as a percentage of all ongoing pregnancies were 21% and 6% respect-

Table 3. Reasons for not aspirating follicles in women where only the perurethral route was used

	Total number of patients	(%)	Total number of follicles	Follicles per patient
Small follicles				
<10 mm	28	(16)	52	1·9
10–14 mm	32	(18)	87	2·7
Size not stated	25	(14)	66	2 6
Difficult access				
Difficult access	32	(18)	97	3·0
Cul-de-sac ovary	1	(1)	4	4·0
High ovary	1	(1)	3	3·0
Mobile ovary	3	(1)	6	2·0
Cyst	1	(1)	1	1·0
Lost aspirates				
Follicle punctured, aspirate lost	14	(8)	17	1·2
Ovulated during procedure	3	(1)	10	3·3
Technical problems				
Poor vision	12	(7)	36	3·0
Blocked needle	1	(1)	2	2·0
Pain				
Pain	7	(4)	12	1·7
Unable to maintain a full bladder	1	(1)	2	2·0
Miscellaneous				
Enough oocytes already	2	(1)	3	1·5
No reason given	12	(7)	25	2·1

ively. From July 1985 the 'take home' baby rate per UDFA was 11%, per ET 14%, and per pregnancy 64%.

Discussion

Our results for perurethral UDFA performed on outpatients compare favourably with other UDFA routes (Riddle *et al.* 1987), and with laparoscopic oocyte retrieval (Jones *et al.* 1984). The aspirating needle is more easily seen with the perurethral route than with the transabdominal transvesical route, and fewer bladder punctures are required because the bladder is entered via the urethra rather than through the abdominal wall.

As operator experience increased with the perurethral route, the frequency with which another route was employed fell. This rate subsequently increased when the direct transvaginal route was introduced and new operators joined the programme. The follicle aspiration rate for the perurethral UDFAs rose with increasing operator experience, and then fell as the number of perurethral procedures declined. The commonest reason for not aspirating follicles was mean follicular diameter of <14 mm. Small follicles are technically more difficult to see and aspirate than the larger follicles but we recom-

Table 4. Pregnancy rates achieved in women where only the perurethral route was used

Year	UDFA procedures	ET procedures		Pregnancies achieved		
	n	*n*	Rate/UDFA	*n*	Rate/UDFA	Rate/ET
1984	6	3	(50%)	0	0%	0%
1985	181	154	(85%)	18	10%	12%
1986	280	218	(78%)	43	15%	20%
1987	63	53	(84%)	16	25%	30%
1988	15	11	(73%)	3	20%	27%

ET = embryo transfers.

Table 5. Pregnancy rate according to number of embryos transferred after perurethral UDFA only (July 1985 onwards)

No. of embryos transferred	No. of ET procedures	Pregnancies achieved	
		n	Rate/ET
1	48	4	(8%)
2	87	13	(15%)
3	91	24	(26%)
4	121	29	(24%)
5	26	10	(39%)

ET = embryo transfer.
UDFA = ultrasound directed follicle aspiration.

mend puncture of all available follicles so far as possible.

The percentage of follicles aspirated was lower in the 91 women where a combination of routes was needed, implying that these women posed particular difficulties. The most frequent reason for changing the route of UDFA was difficulty in reaching all the follicles. Therefore, to maximize the follicle aspiration rate, operators should have experience of the different UDFA routes.

Although the transvaginal route for UDFA is currently more popular than the perurethral route, it has not been shown to be superior. The main advantage is that the ultrasound image of the ovarian follicles is clearer with transvaginal scanning than with transabdominal scanning through a full bladder. During transvaginal UDFA the needle is introduced with the aid of a biopsy guide, whereas perurethral UDFA is a freehand technique These differences make transvaginal UDFA an easier technique to teach and learn.

Much of the discomfort of perurethral UDFA is due to the necessity for a full bladder The intravesical volume can be adjusted if necessary to reduce patient discomfort. Varying the intravesical volume may also help to enhance follicle visibility. Sharp discomfort is felt as the needle passes from the bladder and into the ovary, so the number of posterior bladder wall punctures should be minimized. This also helps to reduce the likelihood of urinary extravasation.

The overall complication rate was low, and no major or long-term morbidity was associated with perurethral UDFA. The occurrence of opioid depression in nine women emphasizes that intravenous pethidine and diazepam should be given in small doses with careful attention to the level of consciousness, and resuscitation equipment should be available. No woman developed urinary or pelvic infections after the procedure, and prophylactic antibiotics were not administered. In contrast, we have had two women who developed pelvic infection after transvaginal UDFA, one of the whom developed a pelvic abscess which required drainage under ultrasound control. This difference between perurethral and transvaginal UDFA probably reflects the fact that the bladder is normally a sterile environment, whereas the vagina is not. Haematuria was the second most common complication associated with perurethral UDFA. Transvaginal UDFA is sometimes associated with vaginal bleeding, although this is easier to control by applying pressure.

UDFA by the perurethral route is an acceptable and efficient method for harvesting oocytes on an outpatient IVF-ET programme It will continue to have a role in units where the vaginal probe is not available, or in women where the vaginal route is not suitable either due to inaccessibility of the ovary by the vaginal route, or in the presence of vaginal infection. Our data demonstrate that the technique gives good results in terms of oocyte retrieval and pregnancy rates, with a low frequency of minor complications.

Table 6. Outcome in 80 pregnancies achieved after perurethral UDFA exclusively

Outcome	No. of pregnancies (*n* = 80) *n* (%)
Live births*	*n* (%)
Singletons	39 (49)
Twins	10 (12)
Triplets	1 (1)
Singleton + ectopic	1 (1)
Early pregnancy failure	
Miscarriage	
Fetus present	4 (5)
Fetus absent	6 (8)
Not known	4 (5)
Ectopic	7 (9)
Preclinical	5 (6)
Neonatal death	
Twins	1 (1)
Triplets	2 (3)

UDFA = ultrasound directed follicle aspiration
* A total of 63 infants

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Thrombin-antithrombin III complex levels in normal pregnancy with hypertensive disorders and after delivery

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Summary. The plasma concentration of the thrombin-antithrombin III-complex (TAT) was investigated during uncomplicated pregnancy in 15 women in the first, 22 in the second and 46 in the third trimester, and in 19 women with hypertensive disorders between 25 and 40 weeks gestation. Eight women at term after a normal pregnancy were studied before the onset of labour and within 60 min and 24 h after delivery. A comparison group of 16 healthy, non-pregnant women was investigated. The mean TAT concentration in normal pregnancies increased significantly in the second and third trimester compared with values in the first trimester and in non-pregnant women. In the group with hypertensive disorders during pregnancy TAT levels were significantly higher than in uncomplicated pregnancies. Within 60 min after delivery a distinct increase of TAT concentrations occurred compared to levels before the onset of labour but the levels had returned to normal by 24 h after delivery. Our findings suggest that an activation of the coagulation system occurs in normal pregnancy. A further activation takes place immediately after delivery. The significantly increased TAT levels in pregnancies with hypertensive disorders suggest a state of chronic disseminated intravascular coagulation leading to an enhanced consumption of and a decreased plasma concentration of antithrombin III.

In normal pregnancy and in pregnancies complicated by hypertension there are major changes in the coagulation system. Previous reports investigated new markers for endothelial injury, clotting, and fibrinolysis, such as fibronectin, antithrombin III (AT III) and alpha 2-antiplasmin, to characterize haemostasis in normal pregnancy and in pre-eclampsia (Weiner & Brandt 1982; Gow *et al.* 1983; Weenink *et al.* 1983; Stubbs *et al.* 1984. Graninger *et al.* 1985). The use of new techniques in this field is of particular interest, since hypertensive disorders in pregnancy seem to cause a state of chronic disseminated intravascular coagulation (DIC). This is suggested by the decrease in platelet count, AT III, plasminogen, alpha 2-antiplasmin, and an increase in fibrin degradation products (Hustin *et al.* 1985; Kobayashi & Terao 1987; Saleh *et al.* 1987).

However, many questions regarding the changes in haemostasis during pregnancy, at delivery and in women with hypertensive dis-

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orders remain unanswered. The direct determination of enzymes during intravascular coagulation is difficult, because of the low concentrations in peripheral blood caused by a rapid formation of protease-inhibitor complexes. These protease-inhibitor complexes represent stable products with a well defined half-life in peripheral blood. The major role of thrombin in triggering the coagulation process by activating platelets and transforming fibrinogen into fibrin is well established. The reaction of thrombin with its major inhibitor, AT III, leads to the formation of a stable complex, which represents the end product of an intravascular activation of the coagulation system. It has been shown that an increase of the thrombin-AT III-complex (TAT) concentration is a sensitive marker for the activation of intravascular coagulation (Blanke *et al.* 1987; Hoek *et al.* 1988; Pelzer *et al.* 1988).

The current study was conducted to determine the concentration of TAT during normal pregnancy, at delivery and in pregnancies with hypertensive disorders.

Subjects and methods

The study comprised 91 women with normal pregnancies (mean age 25·8). None of the women had a history of hypertension or any other disease. All were healthy and had an uncomplicated pregnancy up to the time of admission to the study. Fifteen women were in the first (up to 13 weeks gestation), 22 women in the second (14–26 weeks gestation) and 46 women in the third (27–42 weeks gestation) trimester. The characteristics of the studied groups and birthweights of infants are summarized in Table 1.

In eight women (mean age 26·5) TAT concentrations were measured before the onset of labour and after delivery. The women subsequently had normal, uneventful term pregnancies, uncomplicated labours, spontaneous, vaginal delivery and an uneventful post partum period (mean birthweight 3450 g).

The study group with hypertensive disorders during pregnancy consisted of 19 women between 25 and 40 weeks gestation (mean age 27·5). Twelve were nulliparae (63%), seven were multiparae (34%) and none had a history of hypertension, proteinuria or chronic renal disease before pregnancy. The 19 women were divided into two groups according to the classification of Davey & MacGillivray (1986). Group 1 contained 13 women, who developed gestational proteinuria during pregnancy, diagnosed by a total protein excretion of ≥ 0·03 g/l urine in a 24 h urine collection, but no hypertension. The other six women were classified as pre-eclamptic (group 2) because of the development of gestational hypertension and proteinuria. The diagnosis of gestational hypertension was based on two criteria: a diastolic blood pressure of ≥ 90 mm Hg on two occasions at least 4 h apart or one measurement of ≥ 110 mm Hg.

In addition to the pregnant subjects, a comparison group of 16 non-pregnant healthy women (mean age 25·8 years) with regular menstrual cycles was studied. Oral consent was obtained from all women before blood sampling.

Blood sampling and TAT determination

Blood samples were drawn from the cubital vein using the vacutainer system into clean 10 ml glass tubes containing 1 ml sodium citrate (0·11 mol/l) during routine antenatal examination. In women studied at the time of delivery blood samples were drawn 72 to 6 h before the onset of labour and 15, 30, 60 min and 24 h after delivery through an indwelling cubital venous catheter. The samples were then centrifuged for 10 min at 3000 rpm and the supernatant plasma was stored at −20° C.

Measurement of plasma TAT concentrations used a sandwich ELISA (Enzygnost TAT^R, Behringwerke AG, Marburg, West Germany). Citrated plasma was incubated in tubes coated with a polyclonal rabbit antibody directed against human thrombin. The complex is bound to the surface of the tube via its thrombin component. The plasma is then removed, the tube rinsed and, in a second incubation step, a peroxidase-conjugated rabbit antibody directed against free human AT III is bound to the AT III determinants of the complex on the tube surface. Peroxidase activity was measured subsequently (Hoek *et al.* 1988).

The intraassay coefficient of variation ranged from 4% to 8% and the interassay coefficient of variation from 5% to 10%.

Reference values of TAT were obtained from the report by Dati *et al.* (1988), who examined plasma samples from 307 healthy subjects aged between 16 and 67 years. The reference range of TAT, defined as the range between the 2·5 and 97·5 centile, was 1·0 to 4·1 μgl/l (median value 1·7 μg/l).

Table 1. Characteristics of the groups studied and birthweights of infants

	First trimester (*n* = 15)	Second trimester (*n* = 22)	Third trimester (*n* = 46)	Gestational proteinuria (*n* = 13)	Pre-eclamptic (*n* = 6)
Age (years)	24·9 (4·3)	25·4 (5·0)	26·2 (5·2)	27·7 (4·6)	27·0 (3·9)
Gestational age (weeks)					
At blood sampling	10·1 (1·9)	20·6 (3·8)	34·9 (4·4)	34·2 (4·2)	30·8 (4·0)
At delivery	—	—	39·1 (1·9)	36·7 (3·1)	33·0 (3·4)
(range)	—	—	(27–42)	(31–41)	(28–37)
BP at blood sampling (mmHg)					
Systolic	109 (12)	109 (13)	113 (13)	119 (10)	179 (20)
Diastolic	73 (9)	73 (9)	76 (9)	79 (7)	112 (9)
Proteinuria at blood sampling (g/24 h)	0	0	0	1·8 (1·0)	5·2 (2·4)
Birthweight (g)	—	—	3472 (400)	2936 (676)	1958 (741)

Results are mean (SD)

Statistics

The data are presented as means and standard deviations. Statistical significance was determined by Student's *t*-test for dependent samples. P values <0·05 were regarded as statistically significant.

Results

The mean TAT levels in the non pregnant comparison group (2·6, SD 0·7) and in uncomplicated pregnancies in the first trimester (3·1, SD 1·7) were in the normal range. The mean TAT concentrations in the second trimester (5·0, SD 3·2) and third trimester (4·8, SD 2·0) were statistically significantly higher than in the first trimester and the non pregnant groups (P <0·05). There was no significant difference between the second and third trimester groups (Fig. 1).

In seven of the eight women studied at the time of delivery, plasma TAT concentrations before the onset of labour were similar to those measured in the second and third trimester and varied between 2·7 and 6·0 µg/l; in the remaining woman, TAT level had increased to 21 µg/l 6 h before the onset of labour. Within 60 min after delivery there was a distinct increase in TAT concentrations to well above the normal range in all women, but there was no relation between the time after delivery and the TAT increase; 24 h after delivery plasma TAT levels had returned to levels approximately equal to those before the onset of labour (Fig. 2).

Women with hypertensive disorders during pregnancy developed significantly higher TAT levels (mean 12·1, SD 5·2) compared with those in uncomplicated pregnancy and in the comparison non pregnant group (P <0·0005). Furthermore, plasma TAT levels were statistically significantly higher (P <0·005) in women with hypertension and proteinuria (mean 16·8, SD 4·9) than in those with proteinuria but no hypertension (9·9, SD 3·7) (Fig. 1). There was no effect of parity on TAT levels in the women with hypertensive disorders.

Discussion

Intravascular activation of coagulation results in the formation of thrombin which, in turn, is inactivated by a complex formed with its major inhibitor, AT III. This process leads to the appearance of TAT in peripheral blood (Kobayashi & Terao 1987). Consequently measurement of plasma TAT concentrations allows the detection of an activation of the coagulation cascade. Because TAT has a half-life of only a few minutes, the levels reflect the actual extent of the intravascular activation of coagulation *in vivo* at the time of blood sampling.

In the present study we have shown that in healthy, pregnant women an activation of the coagulation system takes place leading to a significant increase of TAT in second and third trimester. It is well established that AT III remains within normal limits during uncomplicated pregnancy and in chronic hypertension during pregnancy (Weiner & Brandt 1980; Weenink *et al.* 1982; Weenink *et al.* 1983). As a result it can be assumed that during normal pregnancy the production of AT III outweighs its consumption and that any increased production of thrombin by

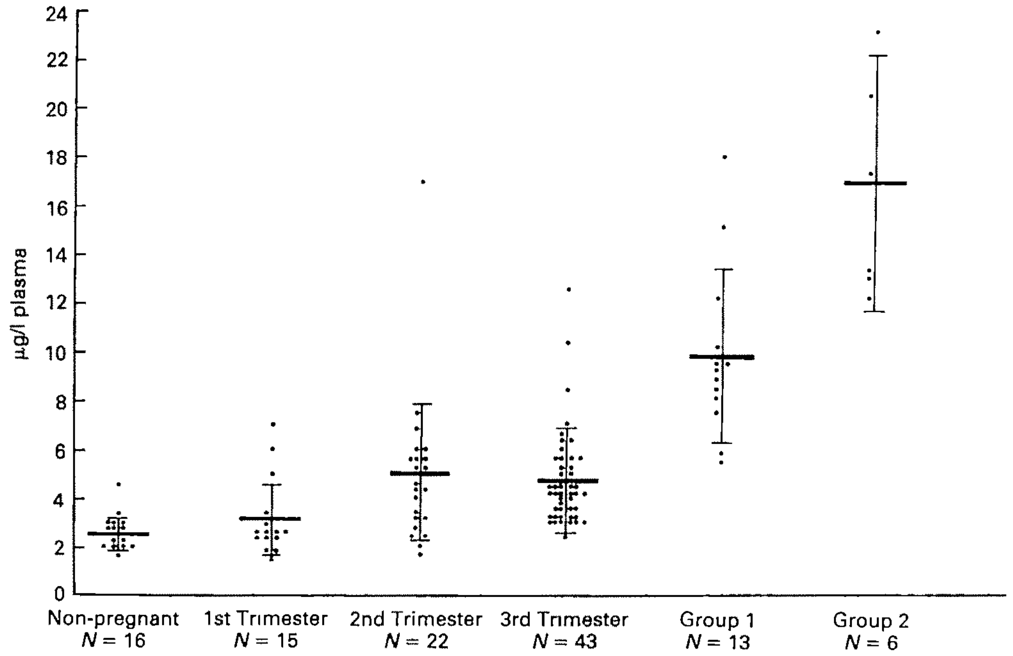

Fig. 1. Individual thrombin-antithrombin III-complex (TAT) levels in non-pregnant women, during normal pregnancy, in women with gestational proteinuria without hypertension (Group 1) and with gestational hypertension and proteinuria (Group 2). Lines indicate mean values and standard deviations

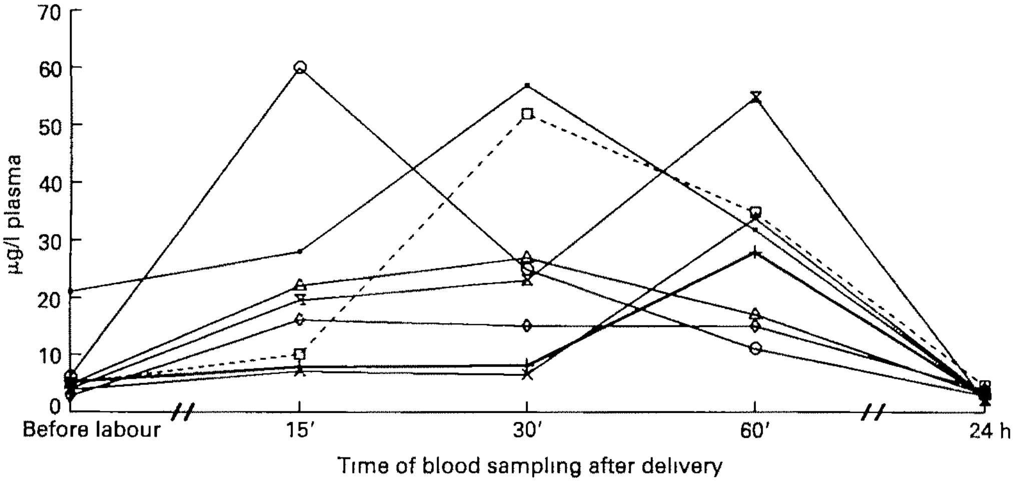

Fig. 2. Thrombin-antithrombin III-complex (TAT) levels before the onset of labour and after delivery in eight women with uncomplicated pregnancies.

transient activation of the coagulation system is inactivated by AT III leading to an increase of TAT levels.

A significant depression of AT III levels occurs in women with pre-eclampsia and gestational hypertension (Weiner & Brandt 1982; Weenink *et al.* 1983; Weenink *et al.* 1984; Weiner *et al.* 1985; Graninger *et al.* 1985). The depression of AT III can be explained by decreased synthesis by the liver, increased urinary loss when proteinuria is evident, a shift to the interstitial compartment and increased intravascular or perivascular consumption. In our study women with gestational hypertensive disorders showed a significant increase of TAT levels. We conclude, that the development of hypertensive disorders during pregnancy causes a state of chronic activation of the intravascular coagulation system. The production of thrombin cannot be totally counteracted by AT III, because the consumption of AT III outstrips its formation resulting in a decrease of AT III levels (Weenink *et al.* 1984; Weiner *et al.* 1985; Saleh *et al.* 1988). Intravascular consumption is likely to be a major cause of AT III depression in women with gestational hypertensive disorders. AT III depression correlates with the degree of maternal and fetal morbidity (Weenink *et al.* 1985). Since the actual extent of the intravascular activation of coagulation can be investigated by measurement of TAT levels, these may provide an additional indicator of the severity of gestational hypertensive disorders.

In uncomplicated pregnancies a significant increase of TAT levels occurred within 60 min after delivery compared with values before the onset of labour; by 24 h after delivery TAT levels decreased to values found before the onset of labour. These data suggest that haemostasis immediately after delivery is supported by an intensive transient activation of the intravascular coagulation system. The increase in TAT levels after delivery reflects the generation of high amounts of thrombin and its inactivation by AT III in the post partum period.

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Twin pregnancy complicated by single intrauterine death. Problems and outcome with conservative management

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Summary. During an 11-year period we encountered 16 pregnancies in which one twin died *in utero* and the pregnancy continued. Eight of these twin pregnancies were monochorionic. None of the women developed severe disseminated intravascular coagulation. The fetal outcome indicates that the prognosis for a surviving dichorionic twin is relatively good, with immaturity the main hazard. By contrast the surviving monochorionic twin has a poor prognosis with a high frequency of neurological damage. This damage is not related to intrapartum or neonatal problems and at present cannot be diagnosed before birth. There is no evidence that birth of the surviving twin by caesarean section will improve the prognosis. Early diagnosis of monochorionic twins and subsequent ultrasound follow up should identify fetal growth discrepancy and possible twin to twin transfusion requiring early delivery.

Ultrasound examinations have shown that death of one twin in the first trimester is relatively common and that the pregnancy usually continues with little adverse effect on the mother and surviving twin (Landy *et al.* 1986).

Death of one twin in the second or third trimester is more serious, with an increased risk for the surviving twin and the possibility of maternal disseminated intravascular coagulation (Hanna *et al.* 1984; Enbom 1985).

The comparative rarity of the condition and the absence of any large study makes it difficult to advise patients on the outlook, and optimum management of these patients is not fully established.

This report presents the results of a conservative policy adopted over the past 11 years.

Patients and methods

We reviewed all twin births at Northwick Park Hospital from January 1977 to December 1988 inclusive. There were 485 twin births over this period, and in 11 (2%) one twin died before the onset of labour. A similar review at Hammersmith Hospital yielded a further five cases. However, these five women had been referred to Hammersmith for management after the diagnosis had been established. As many of the women delivered at Hammersmith are referred from other units it is not realistic to quote an incidence because the base population cannot be defined. Management at the two hospitals was

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similar. After the death of one twin had been confirmed by ultrasound, the pregnancy was allowed to continue until the spontaneous onset of labour, or the development of a clear indication to induce labour or delivery by caesarean section. Maternal antenatal progress was closely monitored, including regular tests for coagulation disorders. The growth and wellbeing of the remaining fetus was assessed by serial ultrasound scans and regular cardiotocograms (CTG).

When the diagnosis was made in labour or at delivery, an attempt was made to estimate the time of fetal death by taking into account the degree of maceration, the autopsy findings and the last ultrasound evidence of fetal life. Possible reduction in fetal movements and lack of maternal weight gain were also considered. Pregnancies where death occurred during labour, or within a week of delivery, were not included in the study. Paediatric records up to the end of follow-up were consulted. An autopsy was performed unless this was against the parents' wish. The placenta was always examined macroscopically and histologically to identify the type of placentation and any abnormality. Swabs were taken from mothers and newborn infants to exclude bacterial infection.

Results

There were 16 pregnancies in which one twin died *in utero* before the onset of labour (Table 1). In four the diagnosis was made only intrapartum or at delivery but these were included because pathological assessment suggested that death had occurred at least one week before delivery. In 8 out of 16 (50%) the twins were monochorionic.

Diagnosis

The diagnosis was suspected when there was a reduction of fetal activity, lack of maternal weight gain or when other obstetric complications developed. The diagnosis was always confirmed by ultrasound. In four pregnancies the diagnosis was not suspected until delivery. In two of these, fetal heart recordings within 24 h of the onset of labour showed two apparently live fetuses. In one of them similar recordings were obtained in labour, although the macerated state of the stillbirths at delivery made it clear that in both cases the traces had been completely misleading.

Maternal complications

Four women had pre-eclampsia and two of them improved temporarily after the death of one twin. One of them had mild activation of coagulation (platelets $80\times10^9/l$, fibrin degradation products >24 <42 mg/l) which resolved after delivery.

Following the death of one twin, five women noticed a reduction in fetal activity, and in six weight gain was reduced or absent. None of the women lost weight after the death of one twin.

In two pregnancies there had been a small antepartum haemorrhage at the time of fetal death, but no evidence of placental abruption could be found at delivery.

Spontaneous preterm delivery followed intrauterine death in 44% of the pregnancies, and in 31% preterm delivery was necessary because of deteriorating maternal or fetal condition.

Fetal and neonatal mortality

In two pregnancies (nos. 3 and 16) the other twin also died *in utero* 3 and 4 weeks, respectively, after the death of the first. In patient no. 16 the twin which survived temporarily showed such severe growth retardation on ultrasound scan that the fetus was not considered salvageable and there was no intervention.

In the second pregnancy (no. 3) although there was growth retardation, daily cardiotocographs (CTGs) were reassuring. At 35 weeks and 2 days, a further ultrasound scan showed an adequate rate of growth and CTGs and fetal activity charts were normal, but 2 days later the fetal heart could not be detected and intrauterine death was confirmed by ultrasound. Labour was then induced with prostaglandins, and at delivery there was a single amniotic sac and the two umbilical cords had become entangled. The umbilical blood flow of the second twin had been obstructed by the formation of a true knot in the cord.

Two babies died in the neonatal period. One (no. 5) had developed severe hyaline membrane disease and died in cardiac failure aged 4 weeks. The other death (no. 15) was due to a combination of immaturity, hyaline membrane disease, intraventricular haemorrhage and infection. Bacterial cultures were positive for

Table 1. Patients' characteristics

Patient no.	Antenatal complications	Gestation at delivery (weeks)	Mode of delivery	Birthweight (g)	Apgar score at 1, 5 min	Placental weight (g)	Findings & follow-up	Autopsy	Estimated time between death & delivery (weeks)
Monochorionic									
1	Pre-eclampsia Preterm labour IUGR twin II	36	S-NVD	2360 1500	8,10 IUD	950	Cerebral atrophy, renal failure	MSB, NGA	2
2	None	37	I-NVD	2440 760	7,10 IUD	650	Spastic quadriplegia	MSB, NGA	7
3	IUGR twin I–II	35	I-NVD	1400 280	IUD IUD	600 Monoamniotic		MSB, NGA cords entangled	3 days twin I 3 weeks twin II
4	Preterm labour IUGR twin II	35	S-NVD	2600 380	7,9 IUD	500	Spastic quadriplegia	NA	6
5	Preterm labour Pre-eclampsia	30	S-NVD	385 720	IUD 2,7	211	Severe HMD Patent Ductus NND @ 4 weeks	Twin I MSB, NGA Twin II cardiac failure	6
6	Pre-eclampsia IUGR twin I	30	CS	1320 960	4,7 IUD	420	Low platelets normal	NA	1
7	Preterm labour	33	S-NVD	1300 1260	IUD 8,9	530	Normal	MSB, NGA	8 days
8	IUGR twin I	32	CS	1540 1820	IUD 9,10	680	Normal	MSB	1
Dichorionic									
9	None	38	S-NVD	2700 2230	7,9 IUD	775	Normal	MSB, NGA	2
10	Preterm labour IUGR twin II	33	S-NVD	2400 680	9,10 IUD	735	Normal	NA	3
11	Preterm labour APH	33	S-NVD	1900 380	5,8 IUD	540	Normal	MSB, NGA	4
12	Pre-eclampsia IUGR twin II APH	35	CS	1740 940	9,9 IUD	600	Normal	MSB, NGA	3
13	IUGR twin II	38	I-NVD	2660 1210	9,10 IUD	640	Normal	NA	5
14	None	38	I-NVD	2640 1960	5,7 IUD	850	Normal	MSB, NGA	2
15	Preterm labour	27	S-NVD	685 900	3,7 IUD	490	IVH, HMD, Listeria infect NND @ 4 days	Twin I–II, Severe, immaturity Listeria infection	1
16	IUGR twin I–II	32	I-NVD	140 480	IUD IUD	175		MSB, NGA Severe IUGR	3 days, twin I 4 weeks, twin II

Abbreviations.
Antenatal complications· APH, antepartum haemorrhage, IUGR, intrauterine growth retardation.
Mode of delivery CS, caesarean section, I-NVD, induced normal vaginal delivery; S-NVD, spontaneous normal vaginal delivery.
Outcome IUD, intrauterine death, NND, neonatal death, HMD, hyaline membrane disease; IVH, intraventricular haemorrhage
Autopsy. MSB, macerated stillbirth; NGA, no gross abnormality, NA, not done

Listeria monocytogenes. Thus by the end of the first month four of the 16 (25%) surviving twins were dead These deaths were equally divided between mono- and dichorionic twins. At autopsy no malformations were detected in any of the twins.

Neonatal morbidity

Three infants (nos. 1, 2 and 4) showed evidence of severe neurological abnormality at follow up. This took the form of severe cerebral atrophy in one and spastic quadriplegia in the other two. All three were monochorionic and in none had there been evidence of intrapartum or postpartum asphyxia. Gestational ages at delivery were 36, 37 and 35 weeks, respectively, and all weighed >2 kg at birth. The remaining nine infants, three monochorionic and all the dichorionic survivors, were normal at follow up.

Discussion

Antepartum death of one twin in the second or third trimester is a rare complication. Enbom (1985) suggested an incidence between 0.5 and 6·8% of all twins, without reference to gestational age at the time of fetal death. The United States Collaborative Perinatal Project suggested an incidence of antepartum death amongst monochorionic twins of 3·7% (Melnick 1977). In the present study 16 pregnancies were identified where one of the twins died *in utero* (2·3%).

A striking difference appears when comparing the outcome of monochorionic and dichorionic twins. Amongst the eight monochorionic twins there were two deaths of the second twin (one stillbirth and one neonatal death), three neurologically abnormal infants (38%) and only three normal survivors (38%). In contrast, eight dichorionic twins were associated with two perinatal deaths of very immature or very growth retarded babies and six normal survivors (75%).

The observed difference between twin types is almost certainly related to placental vascular anastomoses present in a high proportion of monochorionic placentas. Robertson *et al.* (1983) demonstrated vascular connections in 98% of monochorionic placentas. Significant twin to twin transfusion is said to occur in about 15% (Rausen *et al.* 1965), but because of different criteria used in the diagnosis, the true incidence may be substantially higher (Dudley & D'Alton 1986). When this does occur there are serious clinical problems and high perinatal mortality and morbidity. Although twin to twin transfusion was suspected in three monochorionic twins on the basis of growth discrepancies, this could not be proved as none of the surviving twins was anaemic or polycythemic at birth. This does not exclude the diagnosis as one might expect the surviving twin to become normal with passage of time. It is also clear that once the fetus dies *in utero* weight is lost, but there is no available information about the speed or the extent of fetal weight loss after intrauterine death.

The most important finding is the occurrence of neurological abnormality in three infants from monochorionic pregnancies. Melnick (1977) estimated the risk of brain damage in a monochorionic surviving twin at 0·5%. Our data and previous studies summarized in Table 2 suggest that this risk is much higher (26%). Bernischke (1961) was first to describe neurological damage in a surviving twin. He attributed the damage to the passage of thromboplastin from the dead fetus to the surviving twin through placental anastomoses. Yoshioka *et al.* (1979) demonstrated thrombotic occlusion of cerebral arteries in a surviving spastic monochorionic twin, which suggests that disseminated intravascular coagulation (DIC), initiated by the dead twin, could give rise to such damage.

Multiple infarcts may also be caused by sudden changes in blood pressure associated with cord entanglement or occurring at the time of death of one twin (D'Alton *et al.* 1984). Several authors have described a variety of abnormalities in monochorionic survivors and these reports have been summarized by Landy & Weingold (1989). No defects have been reported amongst survivors of dichorionic pregnancies. The maternal hazard of coagulation disorders is stressed in most series. Landy & Weingold (1989), in their review, estimated the risk to be 25%. However, this figure represents only three case reports and may be an overestimate. As for singleton pregnancies, it seems likely that changes only occur after 3–4 weeks (Pritchard, 1959). Maternal DIC was, however, not reported in any series where the management was conservative. Only one mild example occurred in our series and it may have been induced by the pre-eclampsia rather than the retained fetus (no. 6). In our study 13 of 16 women were delivered vaginally. Two caesarean sections were performed because of increasing hypertension (nos. 6 and 11) and one because of

Table 2. Perinatal outcome for surviving monochorionic twins Summary of published cases

Author	No. of cases reported	Morbidity (Neurological)	Mortality
Yoshioka *et al* (1979)	3	3	0
Szymonowicz *et al.* (1986)	6	2	4
Yoshida & Soma (1986)	5	1	0
Carlson & Towers (1989)	9	1	0
Wessel & Schmidt-Gollwitzer (1988)	5	1	0
D'Alton *et al.* (1984)	10	2	0
Enbom (1985)	2	0	0
Romero *et al.* (1984)	1	0	0
Landy & Weingold (1989)	1	0	0
Present study	8	3	2
Total	50	13 (26%)	6 (12%)

lack of growth in the surviving twin (no. 8). Of the 13 vaginal deliveries, labour was induced in five: in two because the other twin had also died, and in three because the surviving twin had reached maturity (37 and 38 weeks respectively). This contrasts with the report by D'Alton *et al.* (1984) who delivered 14 out of 15 such women by caesarean section. The rationale was that the intrauterine environment had led to the death of one twin, and provided the second twin was not grossly immature, delivery was indicated to avoid further damage. In spite of this aggressive approach, two infants showed severe neurological abnormality.

It is not known at what stage brain damage occurs in the remaining monozygotic twin. It is possible that circulatory disturbance and sudden changes in blood pressure occur at the time the first twin dies (Fusi *et al.* unpublished work), and this may be as important as DIC in the resulting morbidity. D'Alton's experience does not suggest that more frequent use of caesarean section would improve the prognosis. This reinforces the view of Bell *et al.* (1986) that liberal use of caesarean section (increased from 3·2 to 50·8%) did not lead to any significant reduction in perinatal mortality or morbidity in twin pregnancies.

Our guidelines depend on identification by ultrasound scan which twins are monochorionic. Several authors have laid down criteria for the diagnosis of chorion type in twin gestation (D'Alton & Dudley 1989; Barss *et al.* 1985), and they should be more widely used. If the twins are monochorionic, frequent assessment should identify growth discrepancy and twin transfusion syndrome. Intervention should then be planned to avoid the death of one or both fetuses. If one twin dies, brain damage to the survivor may not be preventable and the parents should be warned of this possibility. Fetal blood sampling to assess blood gases, coagulation and haematological profiles of the surviving fetus, and to exclude congenital infection or chromosomal abnormalities, may allow more rational management. At present, however, there is no evidence that this will improve the outcome.

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Effects of epidural block with lignocaine and lignocaine-adrenaline on umbilical artery velocity wave ratios

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Summary. Umbilical artery blood velocity A/B ratios were recorded in term fetuses once before and twice after the maternal epidural injection of either 8 ml of lignocaine plain (15 women) or lignocaine with adrenaline 1:200 000 (40 μg) (16 women). The administration of lignocaine plain led to decreases in the ratio of varying degrees in all fetuses regardless of the height of the initial A/B ratio. The injection of lignocaine with adrenaline produced identical results in fetuses with initially normal A/B ratios. In contrast, all six fetuses with initially high A/B ratios (above 2·90) who received the adrenaline-containing anaesthetic reacted with a rise in the ratio, and two of these developed transient heart rate decelerations. Thus, if the initial resistance in umbilical blood flow is high, even the small epidural dose of 40 μg of adrenaline produces a further increase which may be associated with clinical implications.

Perfusion of the fetal placenta can be assessed by measurements of umbilical blood flow velocity waveforms with an Angioscan Doppler spectrum analyzer. The ratio of the systolic peak to the diastolic trough (A/B) is reflective of vascular resistance distal to the point of measurement (O'Rourke 1982). Thus, in the absence of fetal distress, changes in the ratio suggest changes in the umbilical artery blood flow velocity. A recent study of 51 pregnant women admitted to hospital for suspected intrauterine growth retardation confirmed that 'umbilical artery Doppler measurements provide direct and essential information on the adequacy of the placental circulation' (Reuwer *et al.* 1987).

The A/B ratio was found to decline progressively and significantly throughout the last trimester (Schulman *et al.* 1984; Trudinger *et al.* 1985). In 89 normal pregnancies, the ratio decreased from a mean of 2·8 at 29 weeks gestation to a mean of 2·2 at 41 weeks before the onset of labour (Schulman *et al.* 1984). A ratio of 3·0 is considered the upper limit of normal for a term fetus (Fleischer *et al.* 1985; Mansouri *et al.* 1989). Abnormally high ratios have been associated with fetal compromise associated with various clinical disorders (Schulman *et al.* 1984; Trudinger *et al.* 1985).

Decreases in the A/B ratio have been noted

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following epidural analgesia with 2-chloroprocaine for relief of labour pain (Marx *et al.* 1986) as well as following epidural anaesthesia with bupivacaine for caesarean section (Giles *et al.* 1987), but not after epidural administration of chloroprocaine with adrenaline for caesarean section (Veille *et al.* 1988). The present study was designed to compare the effects on umbilical artery velocity waveforms of an epidural anaesthetic with and without adrenaline during labour. We chose lignocaine as the anaesthetic agent, as both the plain and the adrenaline containing forms are commercially prepared.

Subjects and methods

After the study was approved by the medical school's Human Research Committee and patients' informed consent was obtained, 24 primigravidae in the early phase of the active stage of labour (cervix 4–5 cm dilated) participated in the investigation. All were at term. Fetal heart rates and uterine contractions were monitored continuously by external ultrasound and tocodynamometry, respectively. All fetal heart rate patterns were normal with rates ranging from 136 to 154 beats/min. Membranes were intact and remained so during the study period. After intravenous hydration with at least 500 ml of Ringer's lactate solution, umbilical artery flow velocity waveforms were measured by the obstetrician on the team in an interval between contractions with the women in a semilateral position. Thereafter the epidural space was entered at the L3–4 interspace and 4 ml of anaesthetic injected. A catheter was then inserted and the women turned to the opposite side for injection of another 4 ml of the anaesthetic. Five minutes later, they returned to the initial position in which they remained until completion of the study. Twelve of the women received 1·5% lignocaine plain and 12 1·5% lignocaine with adrenaline 1:200 000, chosen in a randomized, double-blind fashion. Randomization was achieved according to Table XVI in Bradford Hill's Principles of Medical Statistics (1971) with even numbers indicating the use of lignocaine plain and odd numbers that of lignocaine-adrenaline. To provide blinding, the solutions were prepared by the senior anaesthetist with their identity unknown to all other members of the team. Top-up doses of local anaesthetic, required more than 45 min after institution of the block, consisted of adrenaline-free drug.

The measurements of umbilical artery blood flow velocity were repeated in the absence of contractions, at 10–12 min (first repeat) and again at 25–30 min (second repeat) after institution of the block. For each of the three velocity examinations, three separate readings were taken, and the calculated average was used for the results All measurements were performed during periods of normal fetal heart rate (136–145 beats/min).

Student's *t*-test, analysis of variation (ANOVA) and the coefficient of variation were employed for the statistical determinations.

Results

The two groups of women were demographically similar. Mean ages were 26·7 (SD 3·6) and 24·6 (SD 1·1) years and mean weights 68·3 (SD 6·1) and 70·4 (SD 4·5) kg, respectively. The differences were not statistically (ANOVA) significant.

All blocks provided good pain relief with sensory levels ranging from T 9–10 to L 1–2. There were no decreases in maternal blood pressure or uterine contractility.

The results of the A/B ratio measurements are depicted in Tables 1 and 2. In those who received plain lignocaine, the initial ratios ranged between 1·73 and 2·70; in those given lignocaine-adrenaline, they ranged from 1·93 to 3·25 (Table 1). Following the epidural block, the

Table 1. Umbilical artery blood velocity A/B ratios before epidural injection of 8 ml of local anaesthetic, 10–12 min later (1st repeat) and 25–30 min later (2nd repeat)

		A/B ratios		
Anaesthetic	*n*	Initial mean (SD) CV	1st repeat mean (SD) CV	2nd repeat mean (SD) CV
Lignocaine plain	12	2·31 (0·28) 12·1	2·22 (0·29) 13·1	2·21 (0·31) 14·0
Lignocaine-adrenaline	12	2·47 (0·34) 13·7	2·41 (0·71) 29·5	2·40 (0·69) 28·8

CV = coefficient of variation percent.

Table 2. Analysis of the umbilical artery blood velocity A/B ratios of 12 women receiving lignocaine-adrenaline according to the normalcy of the initial ratio

No of women	Initial	1st repeat	2nd repeat
	mean (SD)	mean (SD)	mean (SD)
10	2·35 (0·31)	2·10 (0·18)	2·17 (0·21)
1	2·93	3·77	3·25
1	3·25	4·10	4·05

mean ratios declined in both groups but the standard deviations varied notably; in the plain lignocaine group, the standard deviation remained relatively stable whereas in the lignocaine-adrenaline group, it more than doubled. Although these differences did not reach statistical significance, they markedly influenced the coefficient of variation. Analysis of the 12 pregnancies in the lignocaine-adrenaline group (Table 2) revealed that 10 initial ratios were in the range from 1·93 to 2·70 and they decreased after the onset of analgesia. However, in two pregnancies initial ratios were high, 2·93 and 3·25 and both increased further after the block. The first pregnancy resulted in an infant weighing 2550 g and with features associated with prolonged pregnancy; in the second pregnancy intermittent late decelerations (136 → 118 beats/min) developed 12 min after the block and persisted for the next 10 min All 12 infants in this group were born vaginally, in good condition, 3 to 9 h after the study.

To validate the findings in the two pregnancies with high A/B ratios, the study was extended to include seven pregnancies in which the ratios were 3·0 or higher. These pregnancies were complicated by pregnancy-induced hypertension (treated with magnesium sulphate), diabetes mellitus or severe maternal asthma. Four women received 8 ml of lignocaine-adrenaline and three 8 ml of lignocaine plain; randomization and blinding were as described before. As shown in Table 3, use of plain lignocaine was followed by no change or a decline in the A/B ratios. In contrast, administration of the adrenaline-containing anaesthetic uniformly resulted in increased A/B ratios. In one fetus (no. 4), this was accompanied by mild late decelerations for an 8-min period. All four infants had Apgar scores > 7 at 5 min.

The nine pregnancies with initially high A/B ratio were examined by means of ANOVA to determine statistical significance between the group receiving lignocaine with adrenaline and that receiving plain lignocaine. The comparison showed that, although there was no difference initially ($P > 0{\cdot}05$) between the two groups, there was a significant difference at the first ($P < 0{\cdot}001$) and the second ($P < 0{\cdot}025$) repeat A/B measurements. Further inspection revealed that among the group which received no adrenaline, changes in the A/B ratio were not significant ($P < 0{\cdot}25$). In contrast, among the group which was given adrenaline, increases in the A/B ratio were significant ($P < 0{\cdot}001$) at the first repeat measurement but not at the second

Table 3. Umbilical artery blood velocity A/B ratios (A/B), maternal blood pressure (MBP), and fetal heart rate (FHR) before and after epidural injection of 8 ml of local anaesthetic in seven women with initial ratios above 3.0

			Initial			1st repeat			2nd repeat
No.	Anaesthetic	Diagnosis	A/B	MBP (mmHg)	FHR (beats/min)	A/B	MBP (mmHg)	FHR (beats/min)	A/B
1	lign-adren	PIH	3·10	150/90	148	5·00	146/92	148	3·46
2	lign-adren	Asthma	3·08	138/70	136	4·23	130/68	140	3·30
3	lignocaine	PIH + SGA	3·01	140/94	152	2·71	140/92	148	2·70
4	lign-adren	Diabetes	3·10	110/70	140	4·20	110/68	144	3·30
5	lignocaine	Diabetes	3·08	98/52	148	2·76	98/50	154	2·70
6	lignocaine	PIH	3·11	160/90	138	3·10	152/86	144	3·10
7	lign-adren	PIH + SGA	3·57	148/94	150	4·25	140/88	148	3·60

PIH = pregnancy-induced hypertension SGA = small-for-gestational-age Lign-adren = lignocaine with adrenaline repeat measurement, indicating a transient effect of adrenaline.

Discussion

Our study has shown the fetuses with normal umbilical blood flow resistance tolerated the presence of 40 μg of adrenaline added to 8 ml of epidurally injected local anaesthetic solution without untoward incident. However, when the initial resistance in umbilical blood flow was abnormally high, the small dose of 40 μg of adrenaline, a potent vasoconstrictor, produced a further increase. In contrast, the use of plain lignocaine resulted in decreases in the A/B ratio regardless of whether the initial A/B ratio was within or above the normal range.

Like other drugs, adrenaline undergoes systemic absorption from the epidural compartment; the uptake is gradual over a period of 10–15 min and its subsequent breakdown is rapid (Bromage 1978). This time frame explains the delayed and short-lived development of late decelerations in the two pregnancies described. In pregnant sheep, the intravenous injection of adrenaline in a dose as small as 5 μg caused a decrease in uterine blood flow, while fetal heart rate, maternal blood pressure and fetal and maternal blood gas values remained unchanged (Hood *et al.* 1986). In a double-blind randomized human study, 10 healthy women in normal labour received 3 ml of normal saline intravenously while 10 comparable women were given 3 ml of saline containing 15 μg of adrenaline. Fetal distress developed in none of those receiving saline but in two of those given adrenaline. One fetus had late decelerations for 10 min and the other showed mild bradycardia for 4 min. In both, fetal heart rate variability did not return to normal until 20–25 min after the injection. Both fetuses were born vaginally and had normal 5-min Apgar scores (Leighton *et al.* 1987). These results are similar to ours inasmuch as adverse changes in fetal circulation were limited to a minority of pregnancies, lasted less than 30 min and did not affect the condition at birth. The onset of complications was more rapid since the adrenaline had been injected intravenously rather than absorbed from the epidural compartment.

We conclude that, when there is an abnormally high umbilical artery blood flow resistance, the addition of adrenaline to epidurally administered local anaesthetics increases the stress to the fetus.

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The treatment of detrusor instability in postmenopausal women with oxybutynin chloride: a double blind placebo controlled study

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Summary. Idiopathic detrusor instability is a common cause of incontinence in the elderly for which anticholinergic agents are regularly prescribed. Oxybutynin chloride combines anticholinergic action with direct muscle relaxant properties. We performed a double blind placebo controlled fixed dose cross over study of oxybutynin chloride in postmenopausal women suffering from detrusor instability. We found oxybutynin chloride significantly more effective than placebo at reducing the symptoms of urgency and urge incontinence and more effective at reducing the height of the highest unstable detrusor contraction. This was at the expense of an increased residual urine and considerable side effects.

Detrusor instability is the second most common cause of female urinary incontinence and its prevalence increases with age. According to Abrams (1984), 30% of women over the age of 70 who complain of lower urinary tract symptoms have unstable bladders. No underlying cause for the detrusor instability is found in most patients. Treatment, which is often unsatisfactory, is aimed at either improving central control of the voiding reflex or interfering with the innervation of the detrusor muscle.

The bladder contracts in response to stimulation of its parasympathetic nerve supply, consequently drugs with anticholinergic properties are advocated for the treatment of detrusor instability. Unfortunately there are no cholinergic receptors specific to the bladder. Therefore, anticholinergic agents act at all cholinergic receptor sites with the inevitable consequence of predictable anticholinergic side effects.

Oxybutynin chloride is a tertiary amine with combined anticholinergic, muscle relaxant and local anaesthetic properties. It is readily absorbed from the gut and has a plasma half life of 2–3 h although it continues to be effective for up to 6 h (Diokno & Lapides 1972). There have been few studies of this drug in the treatment of detrusor instability and patient groups have been heterogeneous. It has, however, been shown to improve the symptoms of urgency, urge incontinence and frequency in patients with detrusor instability, at the expense of considerable side effects (Moisey *et al.* 1980)

Lower urinary tract symptoms and dysfunction are common after the menopause (Cardozo *et al.* 1987). We decided to investigate the effectiveness of oxybutynin chloride in the treatment of postmenopausal women with idiopathic

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detrusor instability. The study design was double blind placebo controlled cross over using a fixed dose of oxybutynin chloride. It is essential to have a placebo control in any study of detrusor instability as the placebo response is considerable.

Subjects and methods

Neurologically normal postmenopausal women complaining of lower urinary tract symptoms with urodynamically proven detrusor instability were recruited to the study. For the purpose of this study detrusor instability was defined as a detrusor pressure rise of >15 cm of water during filling and provocative cystometry. The abnormal detrusor activity did not need to be associated with incontinence. All the women were postmenopausal which was defined as more than one year since the last menstrual period or from the onset of vasomotor symptoms in those women who had had a hysterectomy.

At entry into the study patients completed a detailed urological and general health questionnaire under medical supervision. All women had sterile urine. The response to treatment was monitored using visual analogue symptom scoring and combined uroflowmetry and videocystourethrography (Bates *et al.* 1970). The symptoms recorded on the visual analogue symptom score were: urgency, urge incontinence, stress incontinence and enuresis.

The study design was double blind placebo controlled cross over. Each patient completed the visual analogue score and had urodynamic tests performed at entry, after the first treatment period and after the second treatment period. The treatment period was 2 weeks with the investigations on the 10th day; between the treatments there was a 2-week wash out period. We used a fixed dose of oxybutynin, 5 mg four times daily, or placebo. The placebo looked exactly the same as the oxybutynin and was composed of microcrystalline cellulose 113·91 mg, ferric colouring agent 0·09 mg (E171 & E172), talc 5 mg, magnesium steaterate 1 mg and film coating.

Table 1. Characteristics of the 37 patients in the two treatment arms of the cross-over study

Variable	Oxybutynin first ($n = 16$)	Placebo first ($n = 21$)
	Mean (SD)	Mean (SD)
Age (years)	58·7 (15)	62·7 (11·5)
Height (cm)	161·0 (3·4)	159·7 (3·3)
Weight (kg)	71·9 (8 5)	71·9 (8·5)
	Median (range)	Median (range)
Parity	2 (0–5)	2 (0–6)

For our study we assumed a placebo response rate of 40% (Taylor & Bates 1979) with a response to oxybutynin of 75% (Moisey *et al.* 1980). A significant difference between placebo and oxybutynin would be expected, with these assumptions, if 22 patients were entered into either arm of a parallel study (44 patients in all). Our study design was cross over. We noted that 7 of 30 patients reported by Moisey *et al.* (1980) dropped out because of side effects. To allow for such patients and for unforeseen problems we planned to enter 40 women into the trial. We put a time limit on the trial, calculated on a historical basis, but were also reliant on the availability of research staff. At the end of the trial we had recruited 37 women. The randomization code was held in the pharmacy and was designed using the toss of a coin for each entry.

Ethics committee approval was sought and given for the study. All patients gave informed consent. The data were computerized and analysed using the Statistical Package for Social Sciences (SSPS). The Wilcoxon matched-pairs sign-ranks test was used for the comparison of paired data.

Results

The study included 37 postmenopausal women, with a mean age of 61 years (SD 13, range 41–87, Table 1). The diagnoses at entry into the study were systolic detrusor instability, provoked detrusor instability, low compliance bladder or a combination of these conditions (Table 2). Five women with provoked detrusor instability had an unstable bladder contraction after coughing.

Table 2. Urodynamic diagnosis at entry into the study

Diagnosis	Number
Systolic detrusor instability	18
Low compliance bladder	5
Provoked detrusor instability	13
(on standing)	(8)
(with a cough)	(5)
Systolic instability plus low compliance	1
Total	37

The other eight in this group had a detrusor pressure rise seen on standing and no other urodynamic abnormality.

Ten women were not investigated whilst taking oxybutynin as they had stopped the medication because of side effects In addition six women did not attend for investigation during oxybutynin therapy and were lost to follow up. All women attended for investigation whilst using the placebo.

There were, therefore, 33 patients who had used the placebo and 21 patients who had used oxybutynin available for analysis (Fig. 1). There were no significant differences in demographic data, symptoms and urodynamic variables between those patients who had placebo followed by oxybutynin therapy and those patients who had oxybutynin therapy followed by placebo. Similarly there were no differences between those patients who dropped out of the study when compared with those who continued, except for the symptom of stress incontinence which was significantly more severe in those patients who dropped out.

Using our study criteria to diagnose detrusor instability, we found that during oxybutynin 13 of the 21 women (62%) were stable after 10 days' treatment. During placebo therapy 14 of the 33 (42%) were stable (Table 3). It is of note that both the active drug and the placebo were very effective at abolishing a detrusor pressure rise seen on standing when there was no other abnormal detrusor activity; also that during placebo treatment, three of four women with low compliance bladders converted to systolic detrusor instability.

When we analysed the different variables used to assess outcome we found that the placebo significantly reduced the symptom of urge incontinence when compared with pretreatment values (Table 4). Oxybutynin therapy significantly reduced the symptoms of urgency, urge incon-

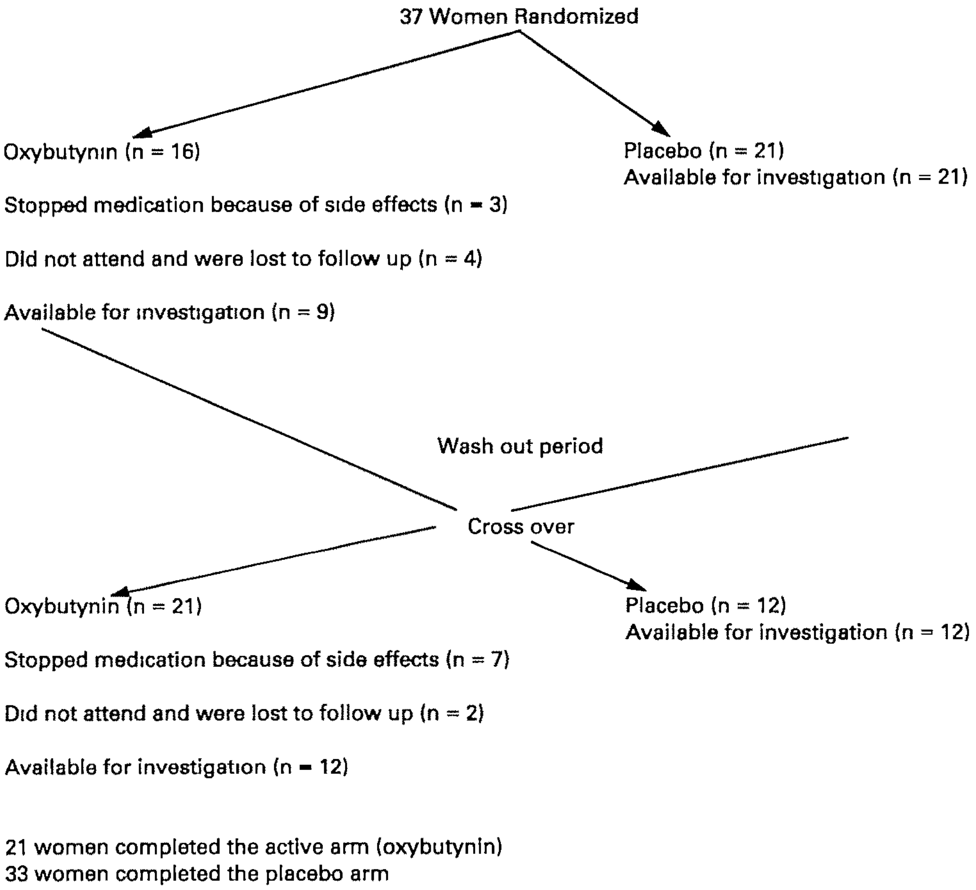
37 Women Randomized
Oxybutynin (n = 16)
Placebo (n = 21)
Available for investigation (n = 21)
Stopped medication because of side effects (n = 3)
Did not attend and were lost to follow up (n = 4)
Available for investigation (n = 9)
Wash out period
Cross over
Oxybutynin (n = 21)
Placebo (n = 12)
Available for investigation (n = 12)
Stopped medication because of side effects (n = 7)
Did not attend and were lost to follow up (n = 2)
Available for investigation (n = 12)
21 women completed the active arm (oxybutynin)
33 women completed the placebo arm

Fig 1. Outcome of the 37 patients entered into the study.

Table 3. Number of women with stable bladders during treatment with oxybutynin or placebo

	Oxybutynin		Placebo	
Symptom at entry	Stable	Total	Stable	Total
Systolic detrusor instability	5	9	5	16
Low compliance bladder	1	3	0	4
Provoked detrusor instability	7	8	8	12
(on standing)	(5)	(6)	(6)	(7)
(with a cough)	(2)	(2)	(3)	(5)
Systolic instability plus low compliance	0	1	0	1
Total	13	21	13	33

There was no significant difference between the two arms

tinence, and enuresis (Table 5). If the changes in visual analogue symptoms scores from pretreatment values, effected by oxybutynin or placebo treatment, were compared, then active therapy was significantly better at improving the symptoms of urgency and urge incontinence (Table 6).

Compared with pretreatment values, placebo treatment significantly reduced the height of the highest unstable contraction and the pressure rise seen during filling cystometry and increased the volume at the first desire to void (Table 4). Active oxybutynin therapy significantly reduced the height of the highest contraction and the pressure rise seen during filling cystometry (Table 5). When the changes from pretreatment values were considered we found that oxybutynin therapy was significantly better than placebo treatment at reducing the height of the highest contraction but this was at the expense of an increased residual urine (Table 6).

Anticholinergic side effects were a considerable problem and partly invalidated the double blind nature of the study. Six women did not attend for investigation while using active therapy and were lost to follow up, the remaining 31 women reported side effects which could be analysed. Dry mouth, dry skin, blurred vision, nausea and constipation were significantly more common during oxybutynin treatment than during placebo treatment. Of the 29 patients who complained of a dry mouth during oxybutynin therapy, 26 thought it was severe (Table 7).

Residual urine was significantly greater with active therapy. If we arbitrarily consider a residual urine of >100 ml to be abnormal, then one of the 33 women investigated during placebo and 7 of the 21 investigated during oxybutynin therapy developed an abnormal residual urine.

Table 4. Pretreatment values compared with values after 10 days treatment with placebo in 33 women

Variable	Before treatment	After treatment
	Mean (SD)	Mean (SD)
Urgency†	65·8 (24·7)	57·4 (30·7)
Urge incontinence†	56·5 (25·7)	38·6 (33·0)*
Stress incontinence†	30·5 (34·4)	25·1 (31·1)
Enuresis†	14·2 (28·0)	8·4 (22·6)
Urodynamic variables		
Residual urine (ml)	20·8 (31·0)	24·1 (47·0)
First sensation (ml)	181·7 (102·8)	213·6 (100·0)*
Cystometric capacity (ml)	383·9 (132·2)	390·5 (110·3)
Pressure rise during filling (cm H_2O)	12·7 (13·0)	7·6 (6·7)*
Highest contraction (cm H_2O)	32·7 (20·2)	18·0 (19·0)*

*$P<0·05$ (Wilcoxon matched-pairs signed-ranks test).
† These symptoms were assessed on a visual analogue symptom scale (score 0–100)

Table 5. Pretreatment values compared with values after 10 days treatment with oxybutinin in 21 women

Variable	Before treatment	After treatment
	Mean (SD)	Mean (SD)
Urgency†	62·4 (25·3)	28·9 (24·7)*
Urge incontinence†	62·5 (24·5)	22·4 (31·6)*
Stress incontinence†	26·3 (37·2)	16·3 (27·6)
Enuresis†	18·7 (33·5)	3·0 (8·1)*
Urodynamic variables		
Residual urine (ml)	21·1 (32·1)	95·1 (157·4)
First sensation (ml)	196·3 (90·2)	276·2 (161·5)
Cystometric capacity (ml)	418·0 (120·9)	478·0 (145·4)
Pressure rise on filling (cm H_2O)	13·6 (15·1)	7·3 (7·9)*
Highest contraction (cm H_2O)	32·8 (20·0)	10·1 (14·1)*

*$P<0·05$ (Wilcoxon matched-pairs signed-ranks test).
† These symptoms were assessed on a visual analogue symptom scale (score 0–100).

Table 6. Change from pretreatment values effected with oxybutynin compared with placebo in 21 women

Variable	Oxybutynin		Placebo
	Mean (SD)	SEM	Mean (SD)
Urgency†	−33·6 (26·4)	7·9*	−7·4 (30·6)
Urge incontinence†	−40·1 (31·8)	7·8*	−24·8 (32·2)
Stress incontinence†	−10·0 (26·2)	5·5	−5·7 (28·5)
Enuresis†	−15·7 (29·6)	5·6	−7·1 (27·6)
Urodynamic variables			
Residual urine (ml)	74·0 (153·6)	33·8*	−6·6 (27·5)
First sensation (ml)	79·9 (196·4)	44·9	25·7 (83·1)
Cystometric capacity (ml)	60·0 (149·0)	36·7	−13·5 (87·9)
Pressure rise on filling (cm H_2O)	−6·3 (10·6)	1·9	−4·5 (13·0)
Highest contraction (cm H_2O)	−22·7 (21·9)	3·5*	−13·1 (22·1)

*$P<0·05$ (Wilcoxon matched-pairs signed-ranks test).
† These symptoms were assessed on a visual analogue symptom scale (score 0–100).

The group who developed a residual urine tended to be older and had longer voiding times.

Six months after the trial 16 of the 21 patients who completed the active arm were contacted. Seven were still taking oxybutynin but all with reduced dosage (3 mg daily to 5 mg three times daily). One patient was controlled with propantheline, one with progesterone (Bessin Laboratories; France) and one with imipramine. Seven were taking no medication and did not want any further therapy.

Discussion

The detrusor muscle contracts in response to stimulation of its parasympathetic nerve supply, therefore anticholinergic agents have formed the most important group of drugs used to treat detrusor instability. Oxybutynin chloride has anticholinergic activity combined with some direct muscle relaxant properties. Studies by Diokno & Lapides (1972) have shown that oxybutynin chloride has a potent action on the bladder and is effective at reducing unstable detrusor contractions. We have found that oxybutynin chloride is effective at reducing the symptoms of urgency, urge incontinence and enuresis in postmenopausal women with idiopathic detrusor instability. Combined with this is a reduction in the height of the highest unstable contraction. The voiding contraction, however, also became less efficient and the residual urine was increased.

At a dose of 5 mg four times daily side effects are very frequent and of the 37 patients entered into the study, only seven continued to take oxybutynin chloride to control their lower urinary tract symptoms 6 months after the study had finished. It appears that we may have chosen too high a dose of oxybutynin for this group of patients. The treatment of detrusor instability with anticholinergic agents is a matter of balancing benefits with side effects. Patients vary markedly in their appreciation of side effects and response to anticholinergic agents. Therefore we feel that in future studies of this or other drugs used for the treatment of detrusor instability a variable dose component should be included in the protocol, despite adding to the complexity of the study.

In our study most of the women who had a detrusor pressure rise on standing, and no other urodynamic abnormality before treatment, became stable during treatment: 5 of 6 during oxybutynin therapy and 6 of 7 during placebo therapy. Instead of being an abnormality, a detrusor pressure rise on standing may be an artefact. We also found that three out of four women with low compliance bladders at the outset converted to systolic detrusor instability during placebo treatment. This supports the possibility that a low compliance bladder can

Table 7. Significant side effects during treatment with oxybutynin compared with placebo in 31 women

Side effects	Oxybutynin	Placebo
Dry mouth	29	10*
Dry skin	13	1*
Blurred vision	8	1*
Nausea	7	0*
Constipation	13	6*

*$P<0·05$ (6 patients did not attend during oxybutynin treatment; see Figure 1)
Other side effects including dry eyes, cough, dry nose, abdominal discomfort and lethargy were equally distributed between the two arms

represent a variant of detrusor instability and is not simply a consequence of tissue stiffness as a result of histological changes.

In conclusion, oxybutynin chloride is an effective treatment for idopathic detrusor instability in postmenopausal women, but a daily dose of 20 mg is associated with very frequent side effects. Treatment should not be discarded because of side effects but the patient should be warned that they may occur and the drug dose should be titrated to produce the maximum benefit with minimum discomfort. Fortunately detrusor instability is subject to spontaneous exacerbations and remissions so that short courses of this relatively unpleasant drug may be all that the patient requires to relieve the worst symptoms.

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Lactation inhibition by a single injection of a new depot-bromocriptine

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Summary. Recently, long-acting injectable forms of bromocriptine have become available for the prevention of lactation. The first developed depot-form was very effective, but had the disadvantage of a slowly metabolized carrier. We investigated the pharmacokinetics, efficacy, tolerance and safety of 40 and 50 mg of a new rapidly eliminated depot-form in 61 postpartum women. Bromocriptine rapidly increased after injection and prolactin was effectively suppressed during the study-period of 60 days. Overall efficacy was very good or good in 98% and no rebound lactation occurred. Sixteen women experienced side effects. Tolerance at the injection site was good and safety tests did not show abnormalities. There were no differences between the two dosages. We conclude that this new depot-bromocriptine is a safe, well tolerated and effective drug in the suppression of prolactin and the prevention of postpartum lactation.

The dopamine agonist, bromocriptine, is a strong inhibitor of prolactin secretion and is used widely for the inhibition of postpartum lactation (Rolland & Schellekens 1973, Rolland 1979, Duchesne & Leke 1981, Barbieri & Ryan 1983). However, the necessity of oral intake during 2 or 3 weeks to avoid rebound lactation tends to limit the compliance of this therapy. Moreover, oral use of bromocriptine is often associated with side effects and oral administration may be impossible in some women with severe puerperal complications.

These problems have led to the development of long-acting injectable forms of bromocriptine. The first one, Parlodel-Long Acting (Parlodel-LA, Sandoz, Basel), contains polylactic acid as a carrier material and has been shown to be a very effective drug in the prevention of puerperal lactation (Peters *et al.* 1986, Rolland *et al.* 1986, Valsamis *et al.* 1987, Defoort *et al.* 1987). However, the metabolization of polylactic acid in the muscle is a slow process, with a half-life of 6 months. Recently a depot-bromocriptine of the second generation has become available, with poly-(D,L) lactide-co-glycolide as carrier material (Parlodel-Long Acting Repeatable (Parlodel-LAR), Sandoz, Basel). The half-life of this carrier is shorter than that of polylactic acid (Rosenthaler 1988, unpublished data) and biodegradation is almost completed within 2 months (Visscher *et al.* 1985).

The aims of this study were to assess the efficacy, tolerance and safety of two dosages (40 and 50 mg active compound) of this new long-acting

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bromocriptine in the prevention of puerperal lactation and to study the pharmacokinetics after either dose of active compound.

Subjects and methods

Healthy postpartum women, who were delivered at term in our hospital and who did not intend to breastfeed their children, were asked to participate in this study. Exclusion criteria were relevant abnormal findings on physical examination, abnormal laboratory values and the use of concomitant treatment that would influence the hormonal or metabolic state. All women remained in hospital for at least 24 h after injection.

Sixty-one women were randomized in two groups (computerized randomization; the dosages were put in numbered envelopes, which were opened after the formal registration of the volunteer). The women received either 40 mg (n=30) or 50 mg (n=31) of the new depot-bromocriptine. The woman did not know the dosage, but the investigator was aware of it because he prepared the suspension just before injection. Each woman gave her informed consent and the protocol had been approved by the ethics committee of our hospital.

At 0900 h, after delivery, a single dose of the new depot-form was injected into the gluteal muscle. This preparation contains bromocriptine in a microcapsulated form, in which bromocriptine mesylate is dispersed in a spherical, amorphous matrix of poly-(D,L) lactide-co-glycolide.

Assessment

Each day during admission and on days 14, 28, 35 and 60 the women were asked about breast symptoms and side effects. In addition, the women recorded daily any breast symptoms, side effects or pain at the injection site, according to the following scoring system: none, mild, moderate (no treatment required) and severe (treatment required). The amount of milk secretion was classified as follows: none, mild (few drops on pressure), moderate (spontaneous secretion) and severe (stream of milk). The daily observations were finally assessed according to the following scale, in which both severity and duration of the symptoms are considered: 'very good': no symptoms or mild short-lasting symptoms (<24h); 'good': mild long-lasting symptoms (>24h) and/or moderate short-lasting symptoms (<24h); 'moderate': moderate long-lasting symptoms (>24h) and/or severe short-lasting symptoms (<24h); 'bad': severe long-lasting symptoms (>24h). The safety of the drug was tested by routine physical examination, ECG and laboratory tests (haemoglobin, platelets, leucocytes and differential count, urea, creatinine and liver enzymes) on day 0 and day 35. Supine and standing blood pressure were measured before injection, 1, 2, 3, 4, 5 and 6 h after injection and on each assessment day.

Serum prolactin (PRL) was measured before injection, 6, 12 and 24 h after injection and on days 14, 28, 35 and 60. In the first 21 women PRL was also measured 1, 2 and 4 h after injection. The half-life of PRL in these women was calculated by describing the individual PRL plots by mono-exponential functions ($PRL_t = ae^{-0{\cdot}693(t-1)} / hl + b$; hl = half-life, t = time in hours, $a = PRL_1 - PRL_{12}$, $b = PRL_{12}$). We also determined serum bromocriptine levels in the first 21 patients, using a specific radioimmunoassay (RIA) with a sensitivity of 0·02 ng/ml (Rosenthaler *et al.* 1983). The Spectria competitive solid-phase RIA from Farmos Diagnostica (Turku, Finland) was used for measuring PRL (sensitivity: 30 mIU/l and inter-assay variation: 9%).

Statistics

Sample size determination was based on an estimated frequency of a 'very good' efficacy in the 50 mg group of 90%. To detect a difference of 25% with a power of 90%, we needed at least 30 women in each group. The Wilcoxon rank sum test was used for analyzing most data. The χ^2 test was used for testing the possible correlation between clinical response and dose. Differences with $P<0{\cdot}05$ were considered significant.

Results

Mean age, body weight and height were respectively 27 (SE 4) years, 75 (SE 10) kg and 166 (SE 6) cm in the 40 mg group and 28 (SE 5) years, 76 (SE 10) kg and 165 (SE 7) cm in the 50 mg group. There were 19 primiparae in the 40 mg group and 17 in the 50 mg group. Four women in the 40 mg group and three in the 50 mg group were delivered by caesarean section. These differences were not significant. All women completed the study as planned.

Bromocriptine and prolactin

Bromocriptine levels rapidly increased after injection (Figure 1). The mean peak concentration and area under the curve (AUC) were significantly higher after the 50 mg dose than after the 40 mg dose (peak: 2·83 (SE 0·45) versus 1·76 (SE 0·26) ng/l, $P=0{\cdot}03$; AUC: 47·6 (SE 3·2) versus 37·1 (SE 3·5) ng/ml.day, $P=0{\cdot}04$). In most subjects there was a small amount of active compound detectable at the end of the study-period (range: 0·02–0·28 ng/ml).

The depot-bromocriptine quickly reduced the PRL level (Figure 2). Within 4 h, PRL decreased to the normal non-pregnant range (100–750 mIU/l). Good fitting mono-exponential curves were used to calculate the half-life of PRL after injection. Mean half-life was 1·1 (SE 0·1) h, there was no difference between the two dosage groups ($P=0{\cdot}99$). PRL was not over-suppressed and remained in the normal non-pregnant range, despite a significant increase on day 28 (mean 706, SE 56) versus 210 (SE 29) mIU/l on day 14, $P<0{\cdot}01$). The PRL level on day 28 was independent of the dose ($P=0{\cdot}50$).

Efficacy

Patients in both groups showed a good clinical response. In the 40 mg group 22 women (73%) had no breast symptoms and six (20%) experienced only mild short-lasting (<24 h) symptoms. Two women (7%) showed moderate symptoms during 1 day. In the 50 mg group we found no breast symptoms in 19 women (61%), mild short-lasting symptoms in five (16%) and short-lasting moderate or long-lasting mild symptoms in six (20%). One of these women was known to have a normoprolactinaemic galactorrhoea before the present pregnancy and had mild symptoms from day 14. One patient in the 50 mg group (3%) experienced severe engorgement, severe pain and moderate milk-secretion on day 3, despite normal PRL. Her complaints coincided with a mild influenza and disappeared after day 6. Most breast symptoms in both groups were noticed during day 2 and 3. Rebound lactation was not observed. On day 28, three women showed very mild breast symptoms together with slightly increased PRL (900, 1500 and 1900 mIU/l). In the 40 mg group, overall efficacy of the treatment was 'very good' in 28 patients (93%) and 'good' in two (7%). In the 50 mg group, overall efficacy was 'very good' in 24 patients (77%), 'good' in six (20%) and 'moderate' in one (3%) (Figure 3). The difference in overall efficacy between the groups was not significant ($P=0{\cdot}16$).

Overall tolerance

Six women in the 50 mg group (19%) and 10 women in the 40 mg group (33%) experienced side effects. Dizziness was recorded most frequently (in 18% of all women; 3% moderate and 15% mild). On the day of injection one woman fainted, but in this patient anaemia was diagnosed and subsequently a blood transfusion was given. Mild nasal congestion was noticed by seven women (11%). One woman showed a mild

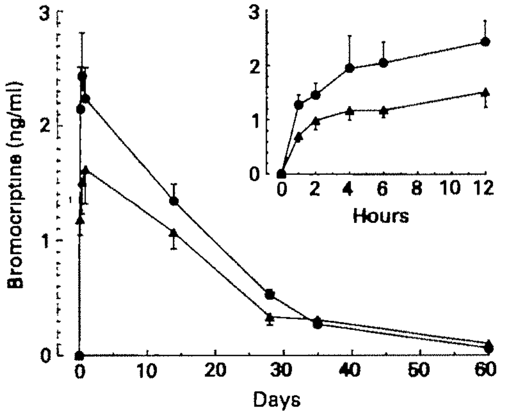

Fig. 1. Serum bromocriptine levels (mean ± SE) in 21 postpartum women after injection of 40 mg (▲) or 50 mg (●) depot-bromocriptine (Parlodel-LAR). The small graph shows the levels of bromocriptine during the first hours after injection.

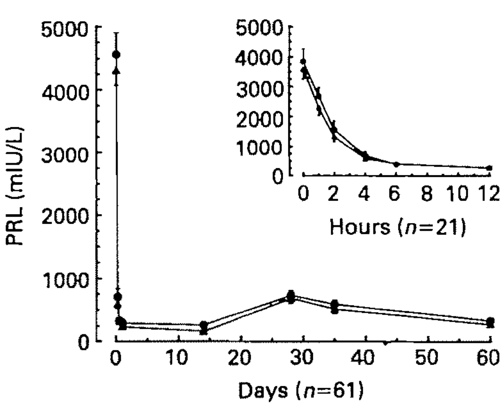

Fig. 2. Serum PRL levels (mean ± SE) in 61 postpartum women after injection of 40 mg (▲) or 50 mg (●) depot-bromocriptine (Parlodel-LAR). The small graph shows the PRL levels of 21 patients during the first hours after injection.

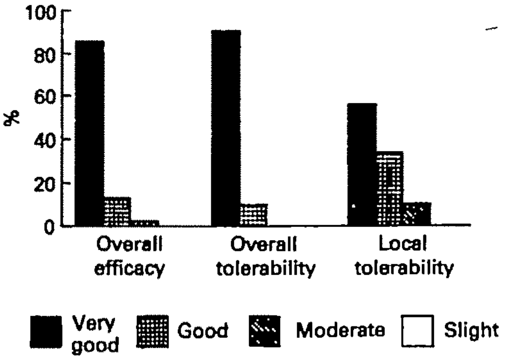

Fig. 3. Final assessment of overall efficacy, overall tolerance and local tolerance in 61 postpartum women after lactation inhibition by a depot-bromocriptine (Parlodel-LAR). There were no significant differences between the 40 mg group and 50 mg group (see text).

facial rash from day 28 till day 42. Most side effects occurred on the day of injection and all disappeared spontaneously. Overall tolerance in the 40 mg group was 'very good' in 26 women (87%) and 'good' in three (10%), while overall tolerance in the 50 mg group was 'very good' in 28 women (90%) and 'good' in three (10%) (Figure 3). These differences between the two groups were not significant (P=0·86).

Local tolerance

Twenty-three women in the 40 mg group (77%) and 18 women in the 50 mg group (56%) recorded pain at the injection site: 24 mild, and 17 moderate. Mild local redness was seen in two and no local rash or deep nodule were observed. All symptoms occurred during the first days and only one woman in the 50 mg group had complaints longer than 3 days. No analgesics were required. Final assessment of the tolerance at the injection site in the 40 mg group was 'very good' in 15 women (50%), 'good' in 13 (43%) and 'moderate' in two (7%), while local tolerance in the 50 mg group was 'very good' in 19 women (61%), 'good' in eight (26%) and 'moderate' in four (13%) (Figure 3). Again no difference between the two groups was found (P=0·31).

Safety

The routine physical examination was in the normal range both before and after treatment and all women had a normal postpartum uterine involution. Blood pressure showed a slight decrease during the first hours after injection but remained unchanged over the following days. No orthostatic hypotension was observed. One patient showed a newly occurring abnormality on her ECG on day 35 (a mild sinus tachycardia, of no clinical relevance). The safety laboratory tests only showed changes which are typical for the puerperium. Before injection, 33 women had an anaemia and in 80% a leucocytosis was seen Marginal eosinophilia was present on day 35 in nine women (15%). No other abnormalities were observed.

Discussion

In this study we investigated for the first time the effectiveness of a second generation depot-bromocriptine (Parlodel-LAR) to suppress PRL secretion and to prevent postpartum lactation.

The performance of the new drug with regard to the kinetics of bromocriptine was satisfactory at both dose levels, although mean levels after 28 days were still considerable. As far as we know, this is the first time that the pharmacokinetics after depot-bromocriptine in postpartum women was studied. Our results correspond grossly with those found after the conventional depot-bromocriptine in normal men (del Pozo *et al.* 1986).

PRL decreased in 4 h to the normal non-pregnant range. This is faster than the decrease observed after oral bromocriptine, which takes 3 days (Rolland 1979). The half-life of PRL after postpartum depot-bromocriptine has not been described until now. The calculated mean half-life of 1·1 h is in agreement with the rapid PRL decline which was observed after the conventional depot-bromocriptine in normal men (del Pozo *et al.* 1986). On day 28, we observed a slight increase of PRL (to the upper part of the normal range), which was accompanied by a mean bromocriptine concentration of 0·33 ng/ml (50 mg dose) and 0·52 ng/ml (40 mg dose). So, these concentrations seemed to be the minimal required levels for adequate PRL suppression in postpartum women. The PRL rebound in our study was smaller than that seen after oral administration (Leleux *et al.* 1981). This may be due to a more gradual decline of bromocriptine levels after depot administration than after stopping oral medication.

There is large experience of what happens when no lactation suppression is attempted. Eight studies compared bromocriptine with placebo (reviewed by Parazzini *et al.* in 1989) and two studies compared bromocriptine with tight binding of the breasts (de Gezelle *et al.* 1979, Shapiro and Thomas 1984). Taken together, the results clearly indicated that bromocriptine is superior to placebo or physical methods (Parazzini *et al.* 1989). Because of these data we did not expose women to placebo treatment.

In comparison with the results of previous placebo studies, our data indicate that the new depot-bromocriptine is a very effective drug in the prevention of puerperal lactation. Rebound lactation, which may be a problem after oral therapy (Rolland & Schellekens 1973, Leleux *et al.* 1981) was not observed at all. The depot-bromocriptine was well tolerated. Dizziness and nasal congestion were the most frequently observed side effects. In contrast with oral bromocriptine studies (Duchesne & Leke 1981, Rolland 1979) we did not observe nausea or vomiting. Bypassing the gastro-intestinal tract may prevent these side effects, by avoiding a possible local gastric effect of bromocriptine (Mehta & Tolis 1979) or by avoiding the first liver passage (Vermesh *et al.* 1988). After the first day, almost no side effects were observed, which may be explained by the rather constant bromocriptine and PRL levels after depot administration, in comparison with the fluctuating levels after oral administration (Thorner *et al.* 1980). Forty-one women experienced some pain at the injection site during the first day(s). It is not clear from our data, whether this is caused by a specific effect of the depot-bromocriptine or by a general effect of an intragluteal injection. The safety tests, including ECG, did not show any relevant abnormalities. The mild eosinophilia we found is not caused by the medication, since it also occurs in untreated postpartum women (Valsamis *et al.* 1987).

We did not study the return of fertility. However, in a previous paper we showed that there is a rapid resumption of ovarian function after postpartum use of depot-bromocriptine (Kremer *et al.* 1989). Accordingly, it is important to inform patients about the possibility of early contraception.

There were no significant differences in PRL levels and clinical results between the two dosage groups. So both dosages seem to be suitable for the inhibition of lactation.

Depot administration has several advantages over oral administration. A single injection gives a better patient's compliance than 3 weeks oral treatment and it requires 50% less drug. Moreover, the parenteral route of administration may be preferable after a caesarean section or in women with severe puerperal complications Furthermore, our results suggest that depot administration is not associated with rebound lactation or gastro-intestinal side effects. A possible disadvantage of depot-administration is its irreversibility, which may be a problem during the occurrence of side effects.

Our clinical results are largely consistent with those obtained from previous studies with long-acting bromocriptine (Rolland *et al.* 1986, Peters *et al.* 1986, Valsamis *et al.* 1987, Defoort *et al* 1987), but in contrast with these reports we used a depot-form with a new carrier, that has a much shorter elimination time. Biodegradation of this carrier is completed after 2 months (Visscher *et al.* 1985) and therefore residues of this carrier are not present for a longer time than necessary for adequate therapy. Therefore, this new depot-form seems to be more suitable for postpartum use than the conventional one, however, further clinical research is necessary to compare these two drugs. Because of the rapid elimination, it is even possible to administer the new drug at monthly intervals, which may be useful in the treatment of pathological hyperprolactinaemia (van't Verlaat *et al.* 1988).

We conclude that a single injection of 40 or 50 mg of this new depot-bromocriptine is a safe, well tolerated and effective treatment in the suppression of PRL levels and the inhibition of postpartum lactation.

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Early recurrent miscarriage: histology of conception products

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Summary. The histopathological appearance of conception products from 44 women with recurrent miscarriage was compared with those obtained from 105 women with sporadic miscarriage. Abnormal villi, suggesting fetal chromosomal abnormalities, were found in 62% of women with a recurrent miscarriage and in 58% of those with sporadic miscarriage. This difference is not statistically significant.

Fetal abnormalities are an important aetiological factor in miscarriage. Boué *et al.* (1975) and Poland & Yuen (1978) observed a frequency of 61·5% fetal chromosomal abnormalities in miscarriage. Until now there have been no large cytogenetic studies on conception products of patients with recurrent miscarriage. This is not surprising, because one can never predict whether women who have had one miscarriage will subsequently have recurrent miscarriages. Despite the high frequency of fetal chromosomal abnormalities in conception products after a miscarriage, routine cytogenetic studies do not seem to be justified at first sight, as the vast majority of these abnormalities arise *de novo* and are not likely to recur in subsequent pregnancies (Boué *et al.* 1975).

However, if recurrent miscarriage were a specific entity with a different aetiology from sporadic miscarriage, it could be hypothesized that fewer fetal chromosomal abnormalities would be found. By studying the villi, the pathologist is able to distinguish between possibly chromosomally normal and possibly chromosomally abnormal pregnancies (Rushton 1987). We know of no study of the histopathology of conception products from women with early recurrent (≥3) miscarriage.

Subjects and methods

This study investigated whether the histopathology of conception products from a population of women with recurrent miscarriage differs from that of a population of women with sporadic miscarriage. The study included 44 women (mean age 30 years) who had had three or more consecutive miscarriages of unknown aetiology. Pregnancy had been confirmed in the past by

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pregnancy tests, ultrasound scans or histological examination.

Miscarriage was defined as the loss of a pregnancy up to 16 weeks from the beginning of the last menstrual period. Of the 44 women, 29 (mean age 28 years) had only had miscarriages (primary recurrent miscarriage group), but 15 women (mean age 31 years) had had one or more children before experiencing their miscarriages (secondary recurrent miscarriage group).

An extensive clinical investigation was performed to rule out infectious, metabolic, anatomical and genetic parental causes. Only couples with normal results were accepted.

These 44 women had experienced 175 miscarriages: 112 in the primary and 62 in the secondnary group. Ectopic pregnancies ($n = 3$) were not excluded since they can be regarded as reproductive failures comparable to miscarriage (Eskes & Van Oppen 1984).

The control group consisted of 105 women (mean age 29 years) who had experienced only one miscarriage before giving birth to a healthy infant.

The histological appearance of the conception products was reviewed by the same pathologist. All specimens were fixed in 4% formalin and embedded in paraffin, after which 4-µm sections were cut. Sections were only considered suitable for review if large numbers of chorionic villi were present. The specimens were divided into three types according to the method described by Rushton (1981; 1987): type I, in which the majority of villi showed microscopic hydatidiform change (this appearance was found by Rushton to show the highest correlation with chromosomal abnormalities); type II, in which the majority of villi showed post-mortem changes of fibrosis; and type III, in which the majority of villi showed a normal aspect and contained vessels in which normoblasts could often be found. This appearance was shown by Rushton to have the lowest correlation with chromosomal abnormalities.

Statistical analysis used the χ^2-test.

Results

There were 127 histological specimens available from 175 miscarriages; review was impossible in 27 because the products of conception consisted merely of decidua. Of the remaining 100 specimens 62 (62%) showed either type I or type II abnormal villi (Table 1).

The results of the histological review of the conception products of the 105 women having sporadic miscarriage (control group) are also shown in Table 1. Of these 105 miscarriages 29 were unsuitable for review because the specimen was inadequate. In 45 of the 76 remaining specimens (59%) abnormal villi of type I or type II were observed. There was no significant difference in the proportion of abnormal villi between the three groups of women.

A fetus or fetal tissue was detected in only 19 (19%) of the 100 samples of conception products from women with recurrent miscarriage that were suitable for review. All the fetuses were malformed but the exact classification of the abnormalities was hampered in all but one case by maceration or by damage sustained during the evacuation procedure. The one fetus that could be given a firm diagnosis had an omphalo-

Table 1. Classification of villi of conception products of women with a primary recurrent miscarriage (PRM) and with a secondary recurrent miscarriage (SRM) and women with a sporadic miscarriage (controls)

	PRM ($n = 29$) n (%)	SRM ($n = 15$) n (%)	Total ($n = 44$) n (%)	Controls ($n = 105$) n (%)
No. of miscarriages	112	63	175	105
No. of conception products available and suitable for review	63 (56)	37 (59)	100 (57)	76 (72)
Histological classification				
Abnormal				
Type 1	30 (62)	9 (62)	39 (62)	29 (59)
Type 2	9	14	23	16
Normal				
Type 3	24 (38)	14 (38)	38 (38)	31 (41)

cèle. The associated villi were abnormal in 10 (53%) of these 19 specimens.

Discussion

Most workers investigating recurrent miscarriage focus their research on aetiological factors of parental origin may institute a variety of therapies (Mowbray *et al.* 1985; Beer *et al.* 1985; Harrison 1985). Officially miscarriage is defined as a pregnancy that ends before the fetus is capable of independent extrauterine survival. The World Health Organization accepted the definitions published by FIGO News (1976) that a miscarriage (spontaneous abortion) is the expulsion of a fetus weighing ≤500 g or before 22 weeks gestation. This definition is useful from an epidemiological but not from an aetiological point of view. Poland & Yuen (1978) studied the histology of conception products in women with recurrent miscarriage (≥2) and concluded that first-trimester miscarriage was more often associated with fetal abnormalities, and second-trimester miscarriage with normal fetal development and maternal abnormality.

Comparison of studies of recurrent miscarriage, especially those involving aetiology and therapy, is hampered by the fact that each country and even each author has used different upper gestation limits. These vary from 16 to 28 weeks. In general, workers have failed to make proper allowance for the possibility that the aetiology of recurrent miscarriage is different from sporadic miscarriage. Histological investigation of the material passed by women admitted to hospital with miscarriage is routine in many centres because of the need to detect hydatidiform mole We suggest that this creates an opportunity for the detection of possible chromosomal abnormalities as a cause for the miscarriage.

In this study, which was part of a thesis which also included the follow-up of the 44 women with miscarriage (Houwert-de Jong 1989), couples were selected for study only if there was no parental abnormality. We found no histological differences in the conception products from women with recurrent miscarriage compared with those from women with a sporadic miscarriage Moreover, the proportions of abnormal villi found in both groups (62% and 58%) are similar to the findings of Boué *et al.* (1975). Of the 44 women with recurrent miscarriage 37 conceived again and 28 (76%) of them had a successful pregnancy without medical intervention (Houwert-de Jong 1989). This also underlines the probability that recurrent miscarriage is no specific entity.

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Successful outcome of pregnancy with severe hypothyroidism. Case report and literature review

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Case report

A 33-year-old white woman was first seen in April 1983 with an 8-month history of lethargy and depression. There were no symptoms specifically suggesting thyroid disease but a very strong family history, with her two elder sisters, mother, four maternal aunts and an uncle all being treated with thyroxine for hypothyroidism. She reported a regular 28-day menstrual cycle and the only significant feature was haematemesis secondary to excessive alcohol consumption.

She weighed 67·8 kg and measured 1·61 m in height. She had a normal sized thyroid gland and no bruit. There were no general abnormalities and she was clinically euthyroid She had a haemoglobin of 13·8 g/dl, with a mean corpuscular volume (MCV) of 101 fl, possibly secondary to her high alcohol intake; biochemistry and liver function tests were normal. The serum thyroxine (total T4) was 91 nmol/l (normal range 60–140), tri-iodothyronine (total T3) 2·7 nmol/l (normal 1·0–2·6), free thyroxine 14·6 pmol/l (normal 9–22), thyroid binding globulin (TBG) 11·3 mg/l (normal 7–17) and thyroid stimulating hormone (TSH) 5·8 mU/l (normal 0·4–5·0). Thus there was almost normal thyroid function. Thyroid microsomal antibodies were detected at a titre of 1:1600.

The patient was referred to a psychiatrist for help with her depression and was asked to return in a year for reassessment of the thyroid status in view of the presence of thyroid antibodies and strong family history. However, she did not attend the clinic and was referred again in September 1986 still complaining of lethargy and now with abnormal thyroid function which had been checked by her general practitioner (total T4 27 nmol/l, total T3 1·0 nmol/l and TSH >60 mU/l). But she failed to attend the clinic.

Interestingly, during the 3 years since her first visit she had had three miscarriages at between 8 and 10 weeks gestation, having conceived easily each time by the same partner. She then conceived again only a month after her general practitioner had found her to be hypothyroid, with her last menstrual period starting on 3/10/1986. At her antenatal booking, at a different hospital, she did not report the family history or possible personal history of thyroid disease. Her booking weight was 79·5 kg, a gain of 11·7 kg in 3 years. The pregnancy was uneventful with a blood pressure fairly constant at 130/80 mmHg, a total weight gain of 11·0 kg and normal fetal growth by ultrasound scan. She went into labour spontaneously at 39 weeks and was delivered by forceps, for fetal distress, of a healthy male infant weighing 3·80 kg. The baby was normal with Apgar scores of 7 and 9 at 1 and 5 min, respectively, and an umbilical vein blood pH of 7·30.

In March 1988 she had conceived again but requested a termination of pregnancy. In May 1988 her general practitioner referred her once again to the thyroid clinic. This time she attended and was found to be grossly hypothyroid, with slow reflexes a pulse of 62/min and weight of 89·4 kg. There was still no goitre. Her haemoglobin was 14·3 g/dl with an MCV of 92·2 fl; biochemistry and liver function were normal. The total T4 was 6 nmol/l (60–140), free T4 1·1 pmol/l (9–22), free T3 1·2 pmol/l (4·3–8·6), TBG 22·5 mg/l (7–17) and TSH 298 mU/l (0·3–3·8). Thyroid antibodies were detected with a titre to the microsomal antigen of 1:25 600 and thyroglobulin of 1:40. She was started on thyroxine replacement therapy, initially at a daily dose of 0·05 mg which was increased to 0·1 mg after a month. She continues on thyroxine and is well, as is her son.

Discussion

This case report illustrates the onset of auto-

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immune thyroid disease over a period of 3 years in a woman who presented with mild symptoms, slightly raised TSH, raised antibodies and a very strong family history of thyroid disease, that is subclinical hypothyroidism. She was menstruating regularly and had three miscarriages during the time when her thyroid function was not known, and when she was also a heavy drinker.

She was then recognized to be severely hypothyroid just before a further conception which resulted in a normal pregnancy and the birth of a healthy infant. One can assume that she was severely hypothyroid during the pregnancy. She then became pregnant for a fifth time, but this pregnancy was terminated. Two months later she was grossly hypothyroid with barely detectable thyroid hormones and a highly elevated TSH level.

At no time was a goitre present and so the diagnosis was probably spontaneous atrophic hypothyroidism. This is an organ-specific autoimmune disease with destruction and atrophy of the thyroid, unlike Hashimoto's thyroiditis, in which lymphoid infiltration causes thyroid enlargement. A rare form of hypothyroidism occurs where circulating antibodies to the TSH receptor have the property of blocking the receptors (Toft 1989). Such antibodies are more usually stimulatory, causing Graves' disease; in both circumstances neonatal problems can result from placental transfer of the antibodies.

It would seem reasonable to extrapolate from the history that our patient became increasingly more hypothyroid. It is known that thyroid function can fluctuate during the time course of autoimmune disease, but there seems no doubt that, at least for her successful pregnancy, she conceived when extremely hypothyroid.

It is a major achievement for a hypothyroid woman to conceive, as the condition is associated with irregular menstruation, menorrhagia and infertility. Plasma progesterone levels are often low leading to persistent endometrial proliferation and bleeding (Ramsay 1986); hyper-prolactinaemia may result from an enhanced response in the pituitary gland to thyrotrophin releasing hormone (TRH). If fertility itself is not impaired, pregnancy is more difficult to maintain in the hypothyroid state (Burrow 1972) with an increased occurrence of miscarriage and stillbirth (Ritchie 1986). The rate of fetal loss is said to be twice normal (Niswander & Gordon 1972), although in that report of 244 pregnancies no distinction was made between treated and untreated women.

In early studies associating reduced thyroid function in women with miscarriage, it was suggested that this was a result and not the cause of the pregnancy loss (Kock *et al.* 1966). However, more recently it has been found that a thyroid profile may be helpful in predicting miscarriage (Winikoff and Malinek 1975). These authors found that the thyroid profile of raised TBG and total T4, reduced T3 resin uptake and constant free thyroxine index is apparent by 4–6 weeks gestation in most healthy women and established by 8–9 weeks in successful pregnancies. However, women with recurrent miscarriage who carried a pregnancy to term attained the profile by 14–15 weeks, and women who miscarried yet again never reached it. They treated four women with recurrent miscarriage with thyroxine throughout six pregnancies which were all successful, and concluded that the failure of thyroxine and TBG to rise from pregestational levels, whatever they were, does not augur well for the outcome of the pregnancy.

It is only in the last 30 or so years that laboratory thyroid function tests have been available and they are much more refined now than in their early days. Therefore first reports of hypothyroidism in pregnancy relied mainly upon a clinical diagnosis, and so the disease was often severe and by 1943 only 16 pregnancies associated with myxoedema had been reported (Hodges *et al.* 1952). They described a myxoedematous woman who conceived six times, was untreated during pregnancy and of her four surviving children only one was normal. Similarly Greenman *et al.* (1962) reported one normal pregnancy out of seven. However, Echt and Doss (1963) reported three cases, one untreated, in which the outcomes were normal and after reviewing the literature they considered that myxoedema did not necessarily increase the frequency of congenital anomalies. This contrasts with the conclusions of Man *et al.* (1958), who found hypothyroid women to have an increased risk of preterm delivery and congenital anomalies. In a review of the literature, Potter (1980) noted that 10·7% of treated and 11·6% of untreated hypothyroid pregnancies resulted in congenitally abnormal surviving infants. Although there is no difference between the two groups, this is a higher incidence than in the general population. Furthermore, if neonatal deaths are included, the rate is 19·2% of live births.

The general frequency of hypothyroidism in pregnancy is 9 per 1000 white women, and 3 per

1000 black women (Ramsay 1989) and for the reasons already mentioned is usually mild. Provided the woman is not iodine deficient her fetus is rarely affected as fetal thyroid function is independent, however, maternal IgG antibody can cross the placenta and cause transient neonatal hypothyroidism (Scott 1986). It is therefore important to assess thyroid status in any pregnant woman where hypothyroidism is suspected, but it should be remembered that the total thyroid hormones may be in the normal nonpregnant range as a result of the doubling of TBG concentration during pregnancy, so free hormone assay or the T3 resin uptake test are used together with the TSH (Ramsay 1989).

Treatment is very important during pregnancy as it has been shown that children born of hypothyroid mothers have lower intelligence quotients at the age of 7 than those born of mothers who received thyroxine during pregnancy (91·9 vs 104·5) (Man 1975).

Patients with untreated hypothyroidism may conceive and continue successfully to term (Montgomery and Harley 1977). Kennedy & Montgomery (1978) reported that fetal thyroid hormone may cross the placenta and improve maternal thyroid status. They described two hypothyroid pregnancies which were untreated and had a normal outcome. At birth there was a fetal to maternal gradient of thyroid hormones, which was said to explain the improvement seen in maternal thyroid function. In the last two decades reviews of pregnancies complicated by hypothyroidism tend to report those diagnosed after conception and then treated with thyroxine. There are few reported cases of pregnancies continuing to term without treatment.

Boylan and Drury (1979) reported three pregnancies in which hypothyroidism was diagnosed in the third trimester, treatment was commenced and the outcome successful in two, with the third resulting in intrauterine death associated with pre-eclampsia at 36 weeks. A similar outcome was reported by Blignault (1980).

Montoro *et al.* (1981) reported the successful outcome of 11 hypothyroid pregnancies. Only four of the 11 were diagnosed before 24 weeks gestation; eight of the 11 pregnancies received thyroid hormone replacement and proceeded normally, although one child had trisomy 21 (maternal age 41 years). Of the three untreated pregnancies one was uneventful, one reverted to euthyroidism by 23 weeks and the third presented at 29 weeks with an intrauterine death and severe pre-eclampsia.

A further series of 25 hypothyroid women followed through 28 pregnancies reported serious maternal and perinatal sequelae, with a high frequency of pre-eclampsia, placental abruption, anaemia, cardiac dysfunction, stillbirths and postpartum haemorrhage (Davis *et al.* 1988). Thyroxine was taken throughout pregnancy in only six of these pregnancies, for between 2 and 38 weeks (with a mean duration of treatment to delivery of 15·5 weeks) in 18 pregnancies and the remaining four received no thyroid replacement therapy. Of the latter, none was uncomplicated, with one stillbirth, three with maternal hypertension and pre-eclampsia and three with postpartum haemorrhage (one requiring hysterectomy), this may be due to the platelet dysfunction and factor VIII deficiency that has been reported in hypothyroidism. In the 28 pregnancies there were three stillbirths and seven infants weighed <2000 g. The outcome was worse in women with overt rather than subclinical hypothyroidism.

The general conclusions drawn from these series were that women presenting in pregnancy with untreated hypothyroidism should be allowed to continue to term, although preferably with thyroxine replacement. Whether correction of thyroid deficiency during pregnancy prevents the adverse sequelae is uncertain.

Pregnancy itself may affect the natural history of thyroid disease. The immunological changes, with a fall in immunoglobulins A and G, ameliorates autoimmune syndromes (Salvi & How 1987). After delivery a rebound phenomenon may result in postpartum thyroiditis. In a recent survey, 11·3% of women assessed at 6 and 12 weeks postpartum were found to have thyroid disease, mostly with transient thyrotoxicosis and goitre, but 1·2% developed long term hypothyroidism (Nikolai *et al.* 1987). In another series primary hypothyroidism was diagnosed after pregnancy in five women with no previous history. Four women had lymphocytic thyroiditis diagnosed by needle aspiration biopsy. All the women were hypothyroid at 6 months postpartum but 5 months later their antithyroid antibody levels had fallen (Fein *et al.* 1980).

Amino *et al.* (1982) reported that in Japan 5·5% of women have thyroid dysfunction after delivery, half of whom have a goitre. In their series of 507 patients 2·6% had transient thyrotoxicosis, which in a further 1·4% was followed by transient hypothyroidism; 1·4% had transient hypothyroidism alone, none had persistent thyrotoxicosis and only 0·2% persistent hypothyroidism. In some women the condition was found to mimic postpartum psychosis, and interestingly there was a fourfold increase in prevalence in women giving birth to girls, leading to the speculation that their immunology may be different.

In summary, it would seem that our patient was already severely hypothyroid when she conceived, and that possibly her earlier miscarriages resulted from thyroid disease. That her pregnancy was successful may have been as a result of amelioration of her disorder resulting from the changes of pregnancy, and a transient state of relative euthyroidism may have existed in the pueperium before she finally presented with gross myxoedema. The long term outlook for her child is not yet known, but there were no initial problems.

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Primary ovarian twin pregnancy. Case report

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Case report

A 27-year-old nulliparous woman attended the casualty department with lower abdominal pain and fainting sensation of a few hours duration. Her last menstrual period had been 7 weeks earlier although she had experienced some painless vaginal bleeding 2 weeks before the admission. She was using a progesterone-only oral contraceptive, the combined pill being contraindicated because of essential hypertension.

On examination she had circulatory collapse with a blood pressure of 70/30 mm Hg. There was marked tenderness and rigidity in her lower abdomen. A provisional diagnosis of ruptured ectopic pregnancy was made and she was transferred immediately to the operating theatre. Blood samples were taken for haemoglobin estimation and six units of blood were cross matched.

A laparotomy performed under general anaesthesia revealed a haemoperitoneum of 2.5 litres. The right ovary was replaced by a haemorrhagic cyst, 6–7 cm in diameter. This was connected to the uterus by the ovarian ligament. The right fallopian tube, the uterus as well as the tube and ovary of opposite side were normal. A right oophorectomy was performed Four units of blood were transfused. She made an uneventful recovery and returned home on the seventh post operative day with a haemoglobin of 10.3g/dl.

Pathology

The ovarian specimen measured 6.5 × 4 × 4 cm. There was a thick cyst measuring 4 × 3 cm which contained two small embryos measuring 8 mm and 9 mm in length, each in a separate thin amniotic sac. The zygosity of the twins could not be ascertained from this specimen. There was some haemorrhage into one of the amniotic sacs.

A corpus luteum was present in the periphery of the cyst. Small cystic follicles were seen in the ovarian cortex. Ovarian stroma, blood clots and chorionic villi were seen in continuity within the cyst capsule which consisted of compressed ovarian stroma.

There was no evidence of endometriosis, decidual reaction or chronic inflammation in the ovary.

Discussion

Ectopic twin pregnancy in the ovary is an extremely rare condition. So far four cases have been reported in the English literature. All four cases were in parous women in their thirties. It seems worthwhile to record a case of ovarian twin pregnancy in a nulliparous woman in her twenties.

The present report fulfils the criteria for an ovarian pregnancy laid down by Spiegelberg (1878).

Modawi (1962) reported the first case which

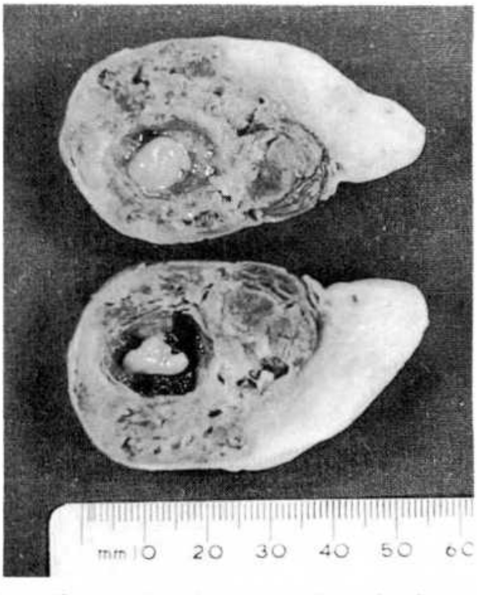

Fig. 1. Cross section of ovarian specimen showing two embryos.

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was a uniovular twin in association with ovarian endometriosis. He commented on the influence of an unfavourable ovarian environment resulting in uniovular twins.

One patient was reported by Green & West (1963), but their search of the literature in the Index Medicus of the previous 20 years did not produce a single case report. That pregnancy was also uniovular and there was extensive endometriosis in the pelvis although ovarian sections did not reveal endometriosis. Subsequently Miller (1965) described a third ovarian twin pregnancy where endometriosis was not detected and it was not possible to state the zygosity of twins.

The patient reported by Kalfayan & Gunderson (1980) was using an IUCD and had a dichorionic twin pregnancy. Lehfeldt *et al.* (1970) estimated approximately one ovarian in 200 ectopic pregnancies but amongst IUCD users the ratio was one ovarian in 9 ectopic pregnancies.

The progesterone-only pill may carry an increased risk of ectopic pregnancy (Liukko *et al.* 1977). This case is the first reported twin pregnancy in association with the progesterone-only oral contraceptive.

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SHORT COMMUNICATIONS

Gamete intrafallopian transfer in women with accessory tubal ostia

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Accessory tubal ostia are not rare (Jeffcoate 1967). They were found to be present in 6% of patients in one series (Beyth & Kopolovic 1982). Such tubal abnormalities are historically associated with tubal pregnancy (Novak & Woodruff 1974). The accessory ostia create a dilemma during the treatment of infertility by gamete intrafallopian transfer (GIFT).

Subjects and methods

The four patients described here all had idiopathic infertility. Laparoscopy had been performed previously in all the patients, and two had also undergone hysterosalpingography.

During the GIFT cycle, pituitary down-regulation was achieved by a daily subcutaneous injection of buserelin (Suprefact, Hoechst UK Ltd, Middlesex, UK), followed by ovarian stimulation with human menopausal gonadotrophins (Pergonal, Serono UK Ltd, Welwyn Garden City, UK). Ovulation was induced with 10 000 iu of human chorionic gonadotrophin (Profasi, Serono UK Ltd) when there were three or more follicles ≥ 20 mm. Laparoscopic oocyte recovery was performed 35 h later.

During the GIFT procedure the fallopian tubes were inspected with the aid of fimbrial forceps. It was at this stage that the presence of an accessory tubal ostium was noted. All were unilateral, involving the right tube, with the accessory ostium 2–4 cm along the tube from the main ostium.

Bilateral GIFT was carried out in three patients. Cannulation of the right tube was first attempted via the main ostium. This resulted in extrusion of the catheter through the accessory ostium. Repeat cannulation through the accessory ostium allowed normal passage of the catheter along the tubal lumen. Two of these three patients conceived and have ongoing singleton pregnancies.

In the fourth patient, the right tube could not be cannulated beyond the junction of the two ostia, and GIFT was carried out on the left side. This patient has an ongoing singleton pregnancy.

Discussion

The frequency of accessory tubal ostia in patients undergoing GIFT in our unit is 5% (4 of 82). All four patients reported here had a longstanding history of primary infertility. The presence of the accessory tubal ostium may have been a causal factor in their infertility—either due to failure of normal ovum pick-up, or due to defective tubal transportation of the ovum (Novak & Woodruff, 1974). Despite previous laparoscopy in all four, the operator had failed to notice this abnormality and the infertility was labelled as idiopathic.

Accessory tubal ostia are not infrequently associated with a blind-ending luminal pouch, and for this reason they may be missed during hysterosalpingography and tubal patency testing at laparoscopy. In contrast to Beyth & Kopolovic (1982) we found the lumen of the accessory ostia encountered in our patients to be in continuity with the proximal tubal lumen.

As GIFT involves manipulation of the tubes, accessory ostia are more likely to be diagnosed during this procedure. Our results show that intrauterine pregnancies can occur in such patients following GIFT. However, fallopian tubes should be inspected carefully before gamete transfer to avoid missing such abnormalities. If an accessory ostium is found, the catheter must be seen to pass beyond the junction of the two ostia to ensure that the gametes are not deposited in a blind pouch.

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Relation between maternal-to-fetal blood glucose gradient and uterine and umbilical Doppler blood flow measurements

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In fetal blood obtained by cordocentesis the mean umbilical vein blood glucose concentration in appropriately grown fetuses is higher than in the umbilical artery, indicating that there is fetal glucose uptake from the placenta (Economides & Nicolaides, 1989). Similarly, the maternal glucose concentration is higher than the fetal and the levels in the two compartments are significantly associated, confirming that the fetus is supplied with maternal glucose (Economides & Nicolaides, 1989). Furthermore, cordocentesis has shown that some small for gestational age (SGA) fetuses are hypoglycaemic and that this is probably not due to decreased gluconeogenesis or increased glucose consumption. A possible mechanism for the low fetal glucose values is reduced utero-placental and/or feto-placental blood flow.

The aim of the present study was to investigate the relation between the maternal to fetal blood glucose gradient (maternal venous minus umbilical vein blood glucose concentration) and Doppler ultrasound measurements of the impedance to flow in the uterine and umbilical circulations in pregnancies with SGA fetuses.

Patients and methods

Uterine artery and umbilical artery flow velocity waveforms (FVWs) were obtained by continuous wave Doppler ultrasound within 30 min before cordocentesis in 30 pregnancies with SGA fetuses. The patients were referred for fetal karyotyping and blood gas analysis because of suspected severe fetal growth retardation. Ultrasound examination in our unit confirmed that the fetal abdominal circumferences were 2·5–10·3 SD below the normal mean for gestation. In all the pregnancies included in this study the fetuses were morphologically and

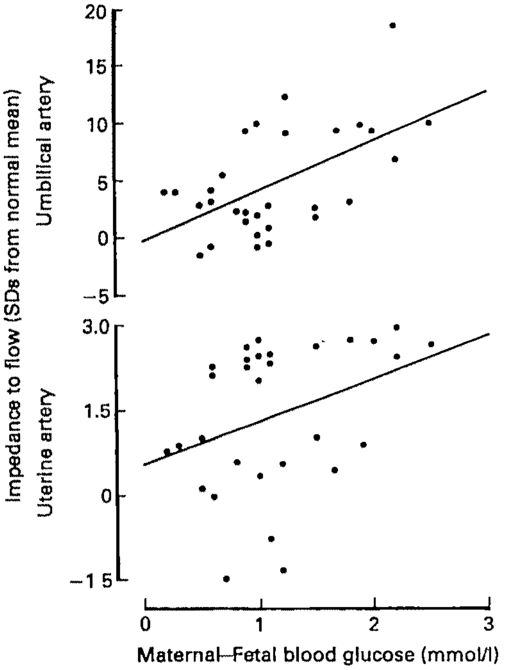

Fig. 1. Relation of maternal to fetal blood glucose concentration gradient and the impedance to flow (in SDs from the normal mean for gestation) in the umbilical and uterine arteries (the diagonal lines are the regression lines).

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chromosomally normal and the diagnosis of SGA was confirmed subsequently by a birthweight below the 3rd centile (Yudkin *et al.*, 1987). Indeed 10 pregnancies ended in perinatal death reflecting the severity of the growth retardation.

FVW were recorded from both the right and left uterine arteries (Aristidou *et al.*, 1990) and umbilical artery (Nicolaides *et al.*, 1988), and the resistance index (RI) and pulsatility index (PI) were calculated respectively, using the Doptek Spectrascan analyser 9000 (Doptek Ltd, Chichester, UK).

Cordocentesis was performed as an outpatient procedure without maternal fasting and sedation or fetal paralysis (Nicolaides *et al.*, 1986). Umbilical vein blood (25μl) was collected using sodium fluoride as an anticoagulant (Vacutainer, Rutherford, New Jersey, USA) and the blood glucose concentration was measured using a Yellow Springs analyser (Yellow Springs Instrument Co, Yellow Springs, Ohio 45387, USA). The blood glucose concentration was also measured in maternal blood taken from an antecubital vein immediately before fetal blood sampling.

Since the uterine artery (UA) RI and the umbilical artery (UmbA) PI change with gestation (Aristidou *et al.*, 1990), the values in the SGA fetuses were expressed as the differences in SDs from the normal mean for gestation (UAΔRI and UmbAΔPI respectively). Regression analysis was used to determine the relation between the maternal to fetal glucose gradient and the UAΔRI and UmbAΔPI. The differences between SGA and AGA pregnancies were tested by the Mann–Whitney *U*-test.

Results

The mean maternal-to-umbilical vein blood glucose gradient in the SGA pregnancies was 1·2 (SD 0·65) mmol/l, which was significantly higher ($z=5{\cdot}52$, $P<0{\cdot}0001$) than the values from 91 pregnancies with AGA fetuses (mean 0·51, SD 0·34 mmol/l), reported by Economides & Nicolaides (1989) and the gradient was significantly associated with both the UAΔRI (Fig. 1; $r=0{\cdot}37$, $n=30$, $P<0{\cdot}05$), and the UmbAΔPI (Fig. 1; $r=0{\cdot}55$, $n=30$, $P<0{\cdot}01$). Multiple regression analysis demonstrated that UmbAΔPI and UAΔRI explain 39·9% of the variance in maternal-to-fetal glucose gradient [gradient = 0·587 + 0·068 (UmbAΔPI) + 0·16 (UAΔRI); residual SD=0·469].

Discussion

Some SGA fetuses have high maternal-to-umbilical vein blood glucose gradient and the degree of hypoglycaemia is proportional to the degree of abnormality in the blood flow impedance measurements in both the uterine and umbilical circulations. These findings provide supportive evidence that fetal hypoglycaemia may result from reduced fetal glucose uptake due to impaired blood flow on both sides of the placenta. However, the degree of fetal hypoglycaemia is associated more significantly with the umbilical than uterine blood flow impairment. This is not surprising in animal studies microsphere embolization of the placenta will only result in growth retardation (Clapp *et al.*, 1980) and reduced glucose uptake (Clapp *et al.*, 1981) when umbilical blood flow is also reduced.

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Artrial natriuretic peptide in fetal disease

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Atrial natriurectic peptide (ANP) is secreted by atrial myocytes in response to increased right atrial pressure. It has potent diuretic and natriuretic properties in addition to causing aldosterone inhibition and peripheral vasodilatation. Animal studies, together with limited observations in humans (Robillard & Weiner 1988), suggest that ANP is particularly active in fetal life. This is a study of ANP in normal fetuses and those complicated by various disease states.

Methods and results

Fetal blood was sampled from the umbilical vein in 38 women as part of clinical management. Gestational age ranged from 18 to 36 weeks and each woman gave informed consent. In 15, the indication was prenatal diagnosis of various conditions for which the fetus was subsequently shown to be unaffected. None was growth retarded, hydropic, anaemic, hypoxaemic or associated with abnormal amniotic fluid volume; these were considered controls. In five, the indication was investigation of non-haemolytic hydrops, whereas in another five with urinary tract anomalies (obstructive uropathy or bilateral multicystic kidney and severe oligohydramnios) the indication was karyotyping.

An additional 0.5 ml of fetal blood was aspirated and transferred directly to chilled EDTA tubes and spun down before storage at −70°C. Pre- and post-transfusion samples were collected in 13 Rh alloimmunized fetuses undergoing 18 intravascular transfusions (one fetus was hydropic at both the first and second transfusions). ANP was measured in batches by pre-extraction radioimmunoassay. Inter- and intra-assay coefficients of variation were 11 and 9% respectively. Fetal acid-base status was compared with published normal ranges (Soothill *et al.* 1986). ANP values in all except the Rh group required log transformation to normalize distributions which were then verified using the Shapiro-Francia W' test. Paired and unpaired *t*-tests were used for within and between group comparison as appropriate.

ANP levels in normal and pathological fetuses are shown in Figure 1. In the control group, ANP levels (geometric mean 16·9 pmol/l, 95% confidence interval (CI) 12·3 to 22·5) did not correlate with gestation. Compared with the control group, ANP was not significantly elevated in four hypoxaemic fetuses (geometric mean 27·2 pmol/l, CI 16·0 to 46·4), five fetuses with uropathies (geometric mean 23·4 pmol/l, CI 14·9 to 38·7), and 16 pre-transfusion samples from 12 non-hydropic normoxaemic Rh alloimmunized fetuses (mean 22·4 pmol/l, CI 17·4 to 27·4). Although mean ANP was significantly higher in the seven samples collected from

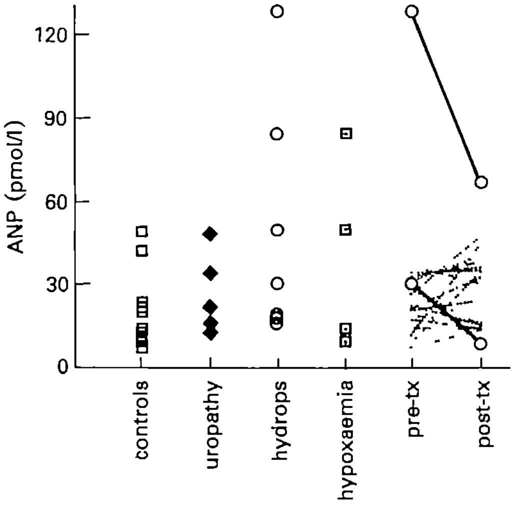

Fig. 1. Basal ANP levels in control fetuses (□), those with uropathies (◆), hydrops (O), hypoxaemic (⊡). Pre- and post-transfusion (tx) levels are shown for hydropic (o———o) and non hydropic fetuses with Rh alloimmunization.

Correspondence. N M. Fisk, RPMS, Institute of Obstetrics and Gynaecology, Queen Charlotte's and Chelsea Hospital, Goldhawk Road, London W6 0XG hydropic fetuses (geometric mean 36·9 pmol/l, CI 24·6 to 55·2, $P<0·05$) compared with the control group, this largely reflects results in two fetuses with very high levels (128·4 and 84·4 pmol/l). ANP increased during ten and fell during six uncomplicated transfusions. The overall change in ANP (mean rise 5·4 pmol/l, CI −1·2 to 12·1) showed no significant correlation with the change in PO_2, the change in haematocrit, or the volume transfused expressed either in ml or as a percentage of fetoplacental volume.

Comment

This study confirms that ANP is present in human fetuses. Although several workers have detected ANP in fetal lambs (Cheung & Brace 1988; Nimrod *et al.* 1988), only one group has reported ANP in normal human fetuses (Robillard & Weiner 1988; Weiner & Robillard 1988) finding levels similar to those in our control group. ANP in fetuses is higher than in children or adults, suggesting that ANP may play an important role during fetal life in the regulation of fluid balance

The pathogenesis of hydrops remains poorly understood. Nimrod *et al.* (1988) reported recently in fetal lambs a 3–4 fold rise in ANP when hydrops was induced by right atrial pacing. However, we found marked elevation of ANP in only two of seven hydropic fetuses. Our findings would not support cardiac failure and volume overload being the mechanism in most hydropic fetuses.

Cheung & Brace (1988) found in sheep that acute hypoxia was the most potent stimulus for fetal ANP release. Our two hydropic fetuses with elevated ANP were also hypoxaemic (see Fig. 1), although ANP was normal in the other hypoxaemic fetuses. This difference in ANP in animal and human hypoxaemic fetuses may reflect the duration of hypoxia.

ANP in fetuses with renal impairment was similar to that in the control group, consistent with the known excretory capacity of the placenta in the regulation of fetal fluid balance.

Although ANP has been reported recently as rising with intravascular bolus transfusion, the effect is often unpredictable, some fetuses having huge rises, whilst in others it actually falls (Weiner & Robillard 1988; Kingdom *et al.* 1989; Panos *et al.* 1989). In our series, although there was an overall rise with transfusion in non-hydropic fetuses, ANP fell during transfusion in six fetuses. We are unable to explain the fall in ANP during transfusion in hydropic fetuses, but another group has recently made a similar observation (Moya & Grannum, personal communication).

Acknowledgments

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Abdominal decompression: new data from a previous study

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The technique of abdominal decompression was developed during the 1950s (Heyns 1959) as a method of optimizing the forces of labour, reducing labour pain and enhancing utero-placental blood flow (Hofmeyr 1990).

The decompression apparatus consists of a plastic suit worn over a rigid frame which allows the pressure surrounding the abdomen to be reduced by up to 100 mmHg. Decompression is controlled by the patient who occludes a vent in the tubing which leads from the suit to a high-flow exhaust pump. This is maintained for 15 s in each minute over 30 min, or during labour to coincide with uterine contractions.

There is some evidence that antenatal abdominal decompression may improve the outcome in certain compromised pregnancies (Hofmeyr 1990). Its value in uncomplicated pregnancies is far less certain. Following a report of higher developmental quotients being measured in children whose mothers had received antenatal decompression than in a non-randomized control group (Heyns 1962), a carefully controlled trial was carried out in the 1960s by the South African National Institute for Personnel Research (NIPR) (Liddicoate 1968). Although the developmental scores (assessed blind to allocation) were very slightly higher in the decompression group at 28 days and at 3 years of age, the differences were not statistically significant.

The perinatal effects of abdominal decompression have been studied using decompression to −70 mmHg as the treatment and to −20 mmHg as the control treatment (Coxon *et al.* 1973). The rate of admission to hospital for pre-eclampsia was similar in the two groups, but the mean duration of hospital stay was shorter in the study group (5·0 *vs* 10·6 days). There was no difference in the mean (SEM) duration of gestation (40·2, SEM 0·09 *vs* 40·1, SEM 0·09 weeks) or birthweight (3250, 30 *vs* 3310, SEM 30 g) between the high and low decompression groups. The placentas were unexpectedly lighter in the high decompression group (627 *vs* 653 g, $P<0·05$). Thus, claims that decompression improves perinatal outcome in uncomplicated pregnancies have not been substantiated. Because of the methodological soundness of the NIPR study (Liddicoate 1968), we have traced the hospital records of women entered in that study and we now report on the perinatal effects of abdominal decompression in uncomplicated pregnancies.

Subjects and methods

Healthy women who attended the antenatal clinic at the Queen Victoria Maternity Hospital, Johannesburg, before 30 weeks gestation were asked to participate in the study (Liddicoate 1968). They were then allocated according to a table of random numbers by an independent member of the NIPR staff either to a study group, in which women were asked to attend for antenatal decompression three times per week from 30 weeks gestation, or to a control group, in which women were asked to attend routine antenatal physiotherapy classes instead. Of 329 women enrolled, 167 were allocated to the decompression and 162 to the control group. Before delivery, 26 and 5 respectively were withdrawn from the study because they had moved house, or failed to attend for treatment, or medical reasons.

We were able to trace the hospital records of 253 (77%) of the original participants in the study. Duration of gestation, birthweight and 1-min Apgar scores were obtained from the case records of these cohorts, and these data were collected without knowledge of the group allocation of each patient. Unfortunately, it was not possible to obtain information on either of the variables for which differences were observed in the trial by Coxon *et al.* (1973), namely hospital admission during pregnancy and placental weight.

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Table 1. Perinatal outcome of pregnancies following allocation to an abdominal decompression and a control (physiotherapy) group

	n	Abdominal decompression	*n*	Control	Odds ratio	95% CI	Significance
Age (years)	123	21·4 (0·3)	126	22·4 (0·4)			
Parous	127	15 (12%)	126	13 (10%)			
Gestation (weeks)	124	39·2 (0·2)	123	39·2 (0·2)			NS
Caesarean section	124	7 (5·6%)	124	2 (1·6%)	3·15	0·84 to 11·0	NS
Assisted delivery	124	19 (15%)	124	16 (13%)	1·22	0·60 to 2·49	NS
1-min Apgar score < 7	121	15 (12%)	121	15 (12%)	1·0	0·47 to 2·14	NS
Birthweight (g)	127	3220 (44)	126	3223 (48)			NS

NS, Not significant.
Results are mean (SEM) values or *n* (%).

Results were compared using Student's test for continuous variables and the odds ratio with 95% confidence intervals (Yusuf *et al.* 1985) for proportions.

Results

The groups available for comparison are comparable in terms of age and parity (Table 1). The gestation at delivery, birthweights, rates of assisted delivery and low Apgar scores in the two groups are strikingly similar. The somewhat higher rate of caesarean section in the decompression group is not statistically significant.

Discussion

Although a proportion (23%) of the hospital records could not be traced, there is no reason to believe that loss to follow-up was in any way selective. We conclude that, in contrast to the possible benefit of abdominal decompression in compromised pregnancies, there is no evidence that its routine use in normal pregnancies improves perinatal outcome.

Acknowledgments

We thank Dr G. Nelson for access to names of patients enrolled in the original study, Dr R. Liddicoate for information about the original study and Dr R. Drubin for permission to examine records from the Queen Victoria Maternity Hospital.

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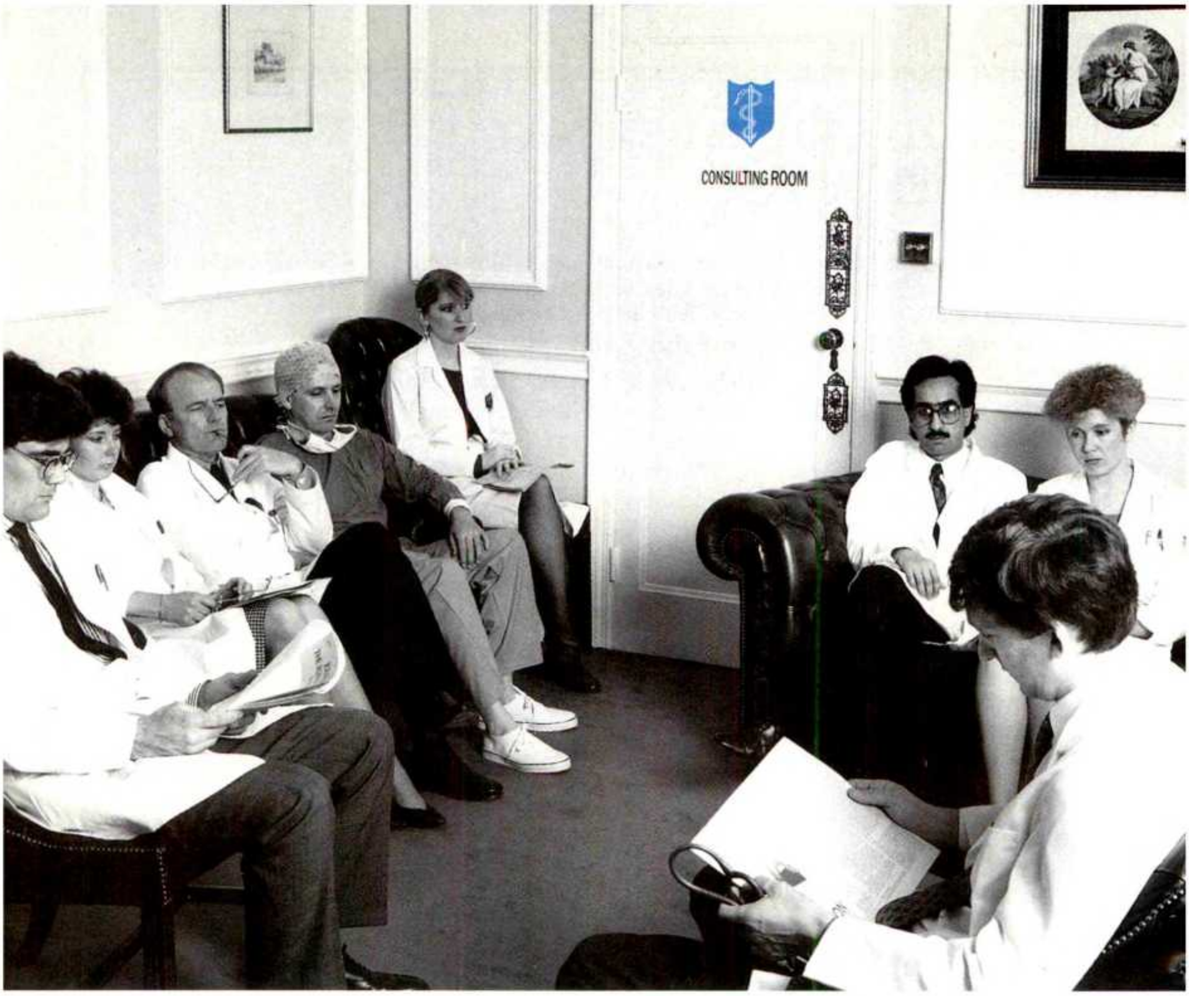

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CORRESPONDENCE

Variation in the measurement of fetal abdominal circumference

Dear Sir,

We were interested to read the recent paper of Sarmandal *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 1261–1265] as we have also completed an inter-observer variation study of the ultrasonic measurement of the fetal abdominal circumference (FAC). We have, however, reached different conclusions. The pertinent details of our study are as follows:

The four radiographers who regularly make FAC measurements within the consultant obstetric unit in Southampton took part in the study. FAC measurements were made by each radiographer, alone and in turn, from 18 women between 32 and 34 weeks gestation. The results were recorded by an independent observer. All measurements were made using a Squibb (Ultramark 4) real time scanner. One measurement of the FAC from each fetus was provided by each radiographer, the selected cross section of the FAC included part of the ductus venosus as it traversed the liver The radiographers were all specialized in obstetric scanning with 1–10 years' experience.

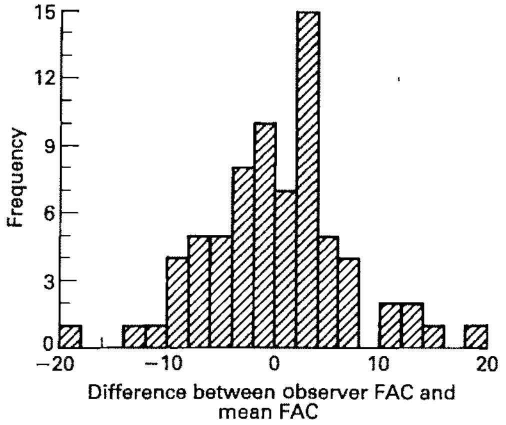

Fig. 1. Distribution of the differences between each observer measurement of the fetal abdominal circumference (FAC) and the overall mean FAC measurement.

The results showed individual coefficients of variation ranging from 2·01% to 2·91% and an overall inter-observer variation of 2·87%. The differences of each measurement from the overall mean are shown in the histogram (Fig. 1). It can be seen that the distribution of the differences is close to normal and the limits of agreement (Bland & Altman 1986) ranged from −18 to +18 mm, similar to those calculated by Sarmandal *et al.* However, such conclusions are only valid when the data are normally distributed and the data of Sarmandal *et al.* do not appear to fulfil this criterion.

In our view, it is also wrong to judge the value of FAC measurements by considering only the limits of agreement between observers. Instead this is more appropriately estimated from the overall statistical relation between the observers; for example, the histogram also shows that 68% of the observations lie within ± 6 mm (ie the 1 SD range). On this basis we have calculated that we can be 95% certain that two measurements are significantly different when they are $\geqslant$15 mm apart, 85% certain when $\geqslant$10 mm apart and less than 70% certain when <5 mm apart (Kringle & Johnson 1986). These considerations can be clinically helpful when repeated measurements of growth are made from the same fetus bearing in mind the expected FAC increase of approximately 10 mm per week or alternatively when a single measurement is compared with an established range.

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Author's reply

Dear Sir,

Thank you for allowing us the opportunity to reply to Mr Wheeler and his colleagues. We were interested that their study of the inter-observer variation of the ultrasonic measurement of fetal abdominal circumference (FAC) produced similar results to ours.

Mr Wheeler suggests that the differences between the observers in our study are not normally distributed; in fact a Shapiro-Francia W' test shows that our data are compatible with a normal distribution (Royston, 1983) so that Mr Wheeler's findings agree with ours: the 95% limits of agreement are approximately ± 18 to 22 mm. We differ in the interpretation of the clinical effects of these limits of agreement. In any form of clinical measurement, for good inter-observer agreement to exist, then *nearly all* the measurement differences should be within an acceptable range, not just some of the differences or even most of them. The 95% limits of agreement provide a 95% data interval, while the 95% confidence intervals (CI) of these limits of agreement indicate the degree of uncertainty with which the limits of agreement of the study are representative of the limits of agreement for the whole population of observers measuring FAC. In medical literature the '95%' concept is now the conventional way of expressing the uncertainty of the results of a study as being representative of the results for a population (for example, odds ratio, relative risk); one does not hear of the '68% CI' or the '85% CI'. Such intervals are therefore inappropriate.

Table 1. Effect of 95% limits of agreement on serial measurements of fetal abdominal circumference (FAC)

Gestational age (weeks)	Mean FAC (mm)	95% limits of agreement (±18mm)
28	253	235 to 271
32	287	269 to 305

We also disagree with Mr Wheeler's views on serial measurements of growth. Table 1 shows the mean FAC at 28 and 32 weeks' gestation (Tamura & Sabbagha, 1980) and the effects of the 95% limits of agreement (Mr Wheeler's data) on the FAC. As can be seen there is an overlap, implying that in a fetus growing at an average rate there may be an interpretation of cessation of growth, with a consequent risk of inappropriate intervention. The fact that serial ultrasound measurements of FAC taken 4 weeks apart are uncertain to be indicative of fetal growth is a testament to the limited clinical usefulness of this technique.

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British Journal of Obstetrics and Gynaecology
June 1990, Vol. 97, pp. 550–551

Listeriosis revisited: the role of the obstetrician

Dear Sir,

After our report of six cases of perinatal listeriosis (Khong *et al.* 1986), we were most interested in the recent report of three similar cases by Buchdahl *et al.* [*Br J Obstet Gynaecol* (1990) **97**, p 186–189] who once again demonstrate the difficulty of making the diagnosis before the fetus is fatally ill. We have recently managed a case of listeriosis where Doppler ultrasound identified fetal abnormality when other more conventional methods of assessing fetal wellbeing remained normal until the baby was severely compromised.

A 32-year-old primigravida presented at 30 weeks gestation with a history of reduced fetal movements. Clinical examination, detailed ultrasound scans, and cardiotocography (CTG) were all normal. Doppler studies showed normal uteroplacental waveforms with an abnormal umbilical artery waveform, suggesting a primary fetal rather than placental problem (Trudinger & Cook 1985). Percutaneous umbilical blood sampling showed normal acid-base status, and no evidence of fetal hypoxia. Results of fetal blood karyotyping and viral studies, were normal. Twenty-four hours later, the patient became pyrexial and there were unprovoked decelerations on CTG. She was immediately delivered by emergency caesarean section of a baby weighing 1·25 kg with Apgar scores of 1 at 1 min and 6 at 5 min. The cord pH at delivery was 7·29 (SBE −4·1). Maternal and neonatal blood culture grew *Listeria monocytogenes,* and both mother and baby made good progress after treatment with ampicillin.

Our patient highlights how misleading conventional means of assessment can be in perinatal listeriosis. Doppler ultrasound assessment of uteroplacental and umbilical artery waveforms may give earlier warning of a primary fetal problem and be a valuable aid to prompt diagnosis.

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British Journal of Obstetrics and Gynaecology
June 1990, Vol. 97, p. 551

Endemic placenta accreta in a population of remote villagers in Papua New Guinea

Dear Sir,

The intriguing account of placenta accreta in the Milne Bay Province of Papua New Guinea by Barss & Misch [*Br J Obstet Gynaecol* (1990) **97,** 167–174] highlights a remarkable variation in the incidence of the condition even within one country. A community based survey of 2225 deliveries (an estimated 80% of all deliveries in the area) in Enga Province in the Papua New Guinea Highlands failed to identify any cases of placenta accreta (Lennox 1984) and in 5 years practice in Enga Province I came across no cases. However, all the maternal deaths in the Enga study resulted from post-partum haemorrhage or retained placenta, highlighting the danger of the third stage of labour.

All the factors postulated by Barss & Misch as contributing to placenta accreta are also present among Enga women except that very high parity is less common than in Milne Bay Province. It may be that very high parity is the main risk factor for this condition.

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British Journal of Obstetrics and Gynaecology
June 1990, Vol. 97, pp. 551–552

Endometrial hyperplasia in an oophorectomized woman receiving tamoxifen therapy

Dear Sir,

I read with interest the paper by Cross & Ismail [*Br J Obstet Gynaecol* (1990) **97,** 190–192]. Readers may be interested to know the outcome of our hysteroscopic follow-up during tamoxifen treatment.

Our findings (Neven *et al.* 1989) confirm significantly more endometrial and endocervical polyps as well as more endometrial hyperplasia in patients taking tamoxifen. Neven *et al.* (1990) assessed 16 breast cancer patients prospectively by hysteroscopy before tamoxifen therapy and again after 6 to 36 months. These results show that the ostrogen-like effect of tamoxifen on vaginal epithelium already reported by Ferrazzi *et al.* (1977) may extend to the uterine mucosa.

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British Journal of Obstetrics and Gynaecology
June 1990, Vol 97, pp 552–553

Large intrauterine haematomata in threatened miscarriage. Frequency and clinical consequences

Dear Sir,

We read with interest the article by Pedersen and Mantoni [*Br J Obstet Gynaecol* (1990) **97**, 75–77]. However, we would consider the rather loose term 'intrauterine haematoma' to be of little use in clinical practice. The exact source of bleeding and the site of the resulting haematoma is not made clear in the article, and these factors would be expected to have a more direct influence on the clinical outcome than the size of such lesions. The article suggests that placental function will not be compromised by a haematoma resulting from haemorrhage from the placental border. However, this assumption cannot be made for massive subchorionic thrombohaematomata (Breus' mole), a condition in which the lesion, which is composed of maternal clotted blood, separates the chorionic plate of the placenta from the villous chorion and is traversed by the main cotyledonary branches of the fetal circulation. The ultrasound appearances of this condition have been described (Almond *et al.* 1983; Oláh *et al.* 1987). Placental separation in the second trimester of pregnancy may result in a severe coagulopathy, and thus may also have important consequences in pregnancy. The resulting coagulopathy is out of proportion to the degree of placental separation at this gestation (Oláh *et al.* 1988). The onset of the coagulation disturbance may be insidious and potentially fatal, and should be excluded in such patients.

In addition, it is unfortunate that histological confirmation of the presence of the haematoma suspected on ultrasound examination was not reported. Placental examination after delivery would have given some indication of the preceding haemorrhage. Without such information it would be difficult to conclude that a small sonarlucent area within the uterus was haematoma and not an artefact. It would also be useful to know how the formula to estimate the volume of these lesions was derived.

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Author's reply

Dear Sir,

We thank Oláh and Gee for their interest in our article. It gives us an opportunity to repeat that the hematomata we observed were located between the membranes and the uterine wall and typically elevated the placental border off the uterine wall, but never tracked beneath the placenta. We never observed an echo-free area within the placenta. Our message was that such large intrauterine haematomata are fairly common in patients with symptoms of threatened miscarriage between 12 and 20 weeks gestation and are benign (of 23 patients one had a miscarriage and two were delivered preterm). The comments by Oláh and Gee about massive subchorionic thrombohaematomata (Breus' mole), a rare and serious phenomenon *within* the placenta which usually occurs in the third trimester of pregnancy, are therefore interesting but of little relevance.

They regret that histological examination of the placentas is lacking, because a small sonarlucent area might have been an artifact. However, their own recent paper does not describe histological examination and our article specifically deals with lesions of 50 ml or more.

Finally, the formula used for volume estimation is that of an ellipsoid of revolution, in which $\pi/6$ has been rounded off to 0·5 instead of 0·52.

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British Journal of Obstetrics and Gynaecology
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BOOK REVIEWS

Conception to Birth: Epidemiology of Prenatal Development (Monographs on Epidemiology of Biostatistics Volume 14) by Jennie Kline, Zena Stein and Mervyn Susser. Oxford University Press, Oxford, 1990, 433 pages with figures and tables, £42.50

Written by three epidemiologists, this book will not only interest those in their own discipline involved in the field of human reproduction but will be of value also to obstetricians who are expected to be able to counsel patients regarding risk factors which may affect the outcome in different aspects of conception and pregnancy.

Five sections review the contribution of epidemiology to the understanding of each of the following: development, conception and early gestation, later gestation, age and parity and the environmental surveillance needed to ensure successful reproduction in the future.

The significance of various teratogens is discussed and the difficulty of associating a particular teratogen with a specific outcome is emphasized. The magnitude of reproductive loss both pre- and post-implantation is well covered and will be of encouragement to those involved in assisted reproduction since the 'take home baby rate' following 'natural' conception must be little better than after 'artificial' conception. A section of the book devoted to environmental factors associated with poor reproductive performance is particularly interesting.

Risk factors involved in pre-term delivery and normal and abnormal intra-uterine growth are well recognized by obstetricians but how these came about is fascinating when viewed purely from an epidemiological point of view.

A plea for future surveillance brings to the reader's attention the need for continued research into reproductive outcome so that the effects of the environment, particularly exposure to chemicals and irradiation as well as social and political changes may be monitored

The book is well produced and easy to read though it requires maintained concentration to follow the arguments and to assess the data. The bibliography is extensive and useful. At £42.50 the book is good value for money containing as it does so much useful information for the specialist obstetrician.

John MacVicar

The Uterine Circulation (Reproductive and Perinatal Medicine (X)) edited by Charles R. Rosenfeld. Perinatology Press, Ithaca, New York. 1989, 312 pages, with figures and tables, list price $104.50 (Prepaid discount price $84.00)

Volume 10 of the series Reproductive and Perinatal Medicine is a monograph devoted to the uterine circulation. The fifteen chapters are contributed by various authors, most chapters originating from North American institutions. The brief introductory chapter is followed by a useful historical overview of important developments in the study of uterine blood flow during this century The remaining thirteen chapters are reviews of specific aspects of the subject. The chapter on functional anatomy includes a lucid summary of current knowledge and deficits of knowledge about the human and ovine placental vasculatures. Three chapters deal with techniques used in the study of placental blood flow: those used in animal studies; studies of labelled steroid clearance in humans; and a description of doppler ultrasound techniques. The chapters on uterine blood flow control during oestrous and early pregnancy, changes in systemic and uterine blood flow during pregnancy, interaction between maternal and fetal placental blood flows, fetal oxygen and nutrient delivery, and the effects on uterine and placental blood flow of the renin-angiotensin and adrenergic systems, steroid hormones and of prostanoids and thromboxane, refer mainly to animal and *in vitro* research. The chapter on circadian changes includes some results of human studies, as does that on exercise. There is inevitably some repetition of material, but each chapter presents a review of its subject which is eminently readable in isolation.

This monograph will serve as a useful summary of current knowledge for researchers in the field of reproductive physiology and a reference for clinicians and clinical researchers with a special interest in conditions in which placental blood flow is of importance, such as preeclampsia and impaired fetal growth. Selected chapters will be worthwhile reading for those preparing for the part I examination for membership of the Royal College of Obstetricians and Gynaecologists, or equivalent examinations.

G. Justus Hofmeyr

ABC of Clinical Genetics by Helen Kingston. BMJ Publication published by the British Medical Association, London. 62 pages with figures and tables, UK £10.95. Abroad £13.00 including air postage

This collection of articles which first appeared in the British Medical Journal, hangs together extremely well to form, perhaps the most readable introductory book to clinical genetics currently available.

There are 15 chapters, about half deal with general topics such as provision of clinical genetic services and risk estimation, and the rest with specific types of genetic disorder. Each chapter is liberally illustrated with clear line diagrams and clinical photographs, which are placed near the text to which they relate.

For those unfamiliar with cytogenetic and molecular genetic techniques, enough information is given in the appropriate chapters to allow understanding of their application to the investigation of human genetic disease. A useful glossary is provided and a list of patient support groups.

There can be few criticisms of this well presented, modestly priced book. It does not pretend to deal in depth with all aspects of the subject, but succeeds in including a remarkable amount of information in only 62 pages.

It can be highly recommended to obstetricians and gynaecologists in training and to those in established practice.

Advances in clinical genetics are rapid, especially in the techniques of DNA analysis and the application to human disease, so it is to be hoped that a second edition of this excellent book will not be too long delayed.

Dian Donnai

Year Book of Obstetrics and Gynecology 1989 edited by Daniel R. Mishell Jr, Thomas H. Kirschbaum and C. Paul Morrow. Year Book Medical Publishers, Inc Chicago, London, Boca Raton 1988, 505 pages, with figures and tables, £40.00

'Non Omnia Possumus Omnes—we cannot all of us do everything. The modern doctor, if he is to stay abreast of the current developments needs at an early stage in his career to go on a speed reading course. I did the 8-month course provided by Lederle Laboratories in about 1965. A further way of keeping up to date is to buy computer discs containing summaries of all the current literature that you are interested in. However the most agreeable way of keeping reasonably up to date is to read the Year Book of Obstetrics and Gynaecology 1989 by Mishell, Kirschbaum and Morrow. This present volume contains 389 articles culled from about 90 scientific journals dating from 1987–8. Articles have mainly been selected because they are of particular clinical relevance even though some of the articles are so unique that the work they describe needs to be repeated before the information gleaned can be applied to daily clinical practice.

This particular year emphasis is on the effect of the Human Papilloma Virus (HPV) on the genital tract with sound clinical advice given about this increasingly-common ailment by Drs Nuovo and Richart. There are excellent chapters on gynaecological urology, infectious diseases and gynaecological oncology; in fact something for everyone no matter what aspect of practice they are interested in.

With this type of volume I prefer to dip into it at random during increasingly rare moments of quiet in a busy clinical day. Without this volume I would not have learnt that premenstrual tension has been treated, like major depressive disorders, by sleep deprivation (pages 459–60). Also only by sampling such a volume does one learn how much research there is going on into the ability of the fetus to hear in utero from 26 weeks onwards. As a result of Year Book 1989 I propose teaching my next grand-child in utero from this age. I may well start by reading him (or her) the 1989 Year Book from cover to cover.

John M. McGarry

Books received some of which may be reviewed at a later date

The Immunology of the Fetus edited by Gérard Chaouat. CRC Press, Boca Raton, Florida, 1990, 320 pages with figures and tables, $120.00

Operative Gynecologic Endoscopy (Clinical Perspectives in Obstetrics and Gynecology) edited by J. S. Sanfilippo and R. L. Levine, Springer-Verlag, Heidelberg, 1990, 325 pages with figures and tables, DM 178

The Causation and Clinical Management of Pelvic Radiation Disease edited by P. F. Schofield and E. W. Lupton. Springer-Verlag, Heidelberg 1989. 258 pages with figures and tables, DM 150

State of Art of the IUD Liber Amicorum Professor M. Thiery edited by H.F.M. van der Pas and Th. O.M. Dieben. Kluwer Academic Publishers, Dordrecht, 1989, 215 pages, Dfl. 150.00, $70.00, £40

Motherhood and Mental Illness 2: Causes and Consequences edited by R. Kumar and I. F. Brockington. Wright, London, Boston, 1988, 294 pages £42.50

Zuspan & Quilligan's Manual of Obstetrics and Gynecology second edition, edited by Jay D. Iams and Frederick P. Zuspan. C. V. Mosby Co. St Louis, 1990, 442 pages with figures and tables, paperback £22.50

Infections in Pregnancy edited by Larry C. Gilstrap, III and Sebastian Faro. Alan R. Liss, Inc. New York, 1990, 277 pages with figures and tables $58.00

International Travel and Health: Vaccination Requirements and Health Advice. World Health Organization, Geneva, 1990, 89 pages Sw fr. 14

Monitoring of National AIDS Prevention and Control Programme: Guiding Principles (WHO AIDS Series No 4) World Health Organization, Geneva, 1989, 26 pages, Sw fr. 8

Obstetrics (Colour Aids) by D. K. James and M. Pillai. Churchill Livingstone, Edinburgh, 1990, 145 pages, 245 illustrations, £6.50

Spermatoza: The Probable Etiology of Gonorrhea, Nonspecific Urethritis and Other Diseases by Donald E. Tyler. Discovery Books, 1990, 87 pages $25. Available from Discovery Books, P.O. Box 285, Ontario, Oregon 97914, USA

Proceedings and Symposiums

Current Concepts in Endometriosis (Progress in Clinical and Biological Research. vol 323) edited by Dev R. Chadha and Veasy C. Buttram Jr. Proceedings of the Second International Symposium on Endometriosis held in Houston, Texas, May 1989. Alan R. Liss, Inc. New York, 480 pages with figures and tables. No price given

Human Genetic Information: Science, Law and Ethics (Ciba Foundation Symposium 149) edited by D. Chadwick, G. Bock and J. Whelan. John Wiley and Sons, Chichester, 1990, 211 pages. £39.95

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The Standardization of Terminology of Lower Urinary Tract Function

Produced by the International Continence Society Committee on Standardization of Terminology

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The Standardization of Terminology of Lower Urinary Tract Function

Produced by the International Continence Society Committee on Standardization of Terminology

Members: Paul Abrams, Jerry G. Blaivas, Stuart L. Stanton and
Jens T. Andersen (Chairman)

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The standardization of terminology of lower urinary tract function

1. Introduction

The International Continence Society (ICS) established a committee for the standardization of terminology of lower urinary tract function in 1973. Five of the six reports (Abrams *et al.* 1986; Bates *et al.* 1976, 1977, 1980, 1981) from this committee, approved by the Society, have been published. The fifth report on 'Quantification of urine loss' was an internal ICS document but appears, in part, in this document.

These reports are revised, extended and collated in this monograph. The standards are recommended to facilitate comparison of results by investigators who use urodynamic methods. These standards are recommended not only for urodynamic investigations carried out on humans but also during animal studies. When using urodynamic studies in animals the type of any anaesthesia used should be stated. It is suggested that acknowledgment of these standards in written publications be indicated by a footnote to the section 'materials and methods' or its equivalent, to read as follows:

'Methods, definitions and units conform to the standards recommended by the International Continence Society, except where specifically noted.'

Urodynamic studies involve the assessment of the function and dysfunction of the urinary tract by any appropriate method. Aspects of urinary tract morphology, physiology, biochemistry and hydrodynamics affect urine transport and storage. Other methods of investigation such as the radiographic visualization of the lower urinary tract are useful adjuncts to conventional urodynamics.

This monograph concerns the urodynamics of the lower urinary tract.

2. Clinical assessment

The clinical assessment of patients with lower urinary tract dysfunction should consist of a detailed history, a frequency/volume chart and a physical examination. In urinary incontinence, leakage should be demonstrated objectively.

2.1 *History*

The general history should include questions relevant to neurological and congenital abnormalities as well as information on previous urinary infections and relevant surgery. Information must be obtained on medication with known or possible effects on the lower urinary tract. The general history should also include assessment of menstrual, sexual and bowel function, and obstetric history.

The urinary history must consist of symptoms related to both the storage and the evacuation functions of the lower urinary tract.

2.2 *Frequency/volume chart*

The frequency/volume chart is a specific urodynamic investigation recording fluid intake and urine output per 24-h period. The chart gives objective information on the number of voidings, the distribution of voidings between daytime and night-time and each voided volume. The chart can also be used to record episodes of urgency and leakage and the number of incontinence pads used. The frequency/volume chart is very useful in the assessment of voiding disorders, and in the follow-up of treatment.

2.3 *Physical examination*

Besides a general urological and, when appropriate, gynaecological examination, the physical examination should include the assessment of perineal sensation, the perineal reflexes supplied by the sacral segments S2–S4, and anal sphincter tone and control.

3. Procedures related to the evaluation of urine storage

3.1 *Cystometry*

Cystometry is the method by which the pressure/volume relationship of the bladder is measured. All systems are zeroed at atmospheric pressure. For external transducers the reference point is the level of the superior edge of the symphysis pubis. For catheter-mounted transducers the reference point is the transducer itself.

Cystometry is used to assess detrusor activity, sensation, capacity and compliance.

Before starting to fill the bladder the residual urine may be measured. However, the removal of a large volume of residual urine may alter detrusor function especially in neuropathic disorders. Certain cystometric parameters may be significantly altered by the speed of bladder filling (see 6.1.1.4).

During cystometry it is taken for granted that the patient is awake, unanaesthetized and neither sedated nor taking drugs that affect bladder function. Any variations should be specified.

Specify

(a) Access (transurethral or percutaneous).
(b) Fluid medium (liquid or gas).
(c) Temperature of fluid (in °C).
(d) Position of patient (e.g. supine, sitting or standing).
(e) Filling may be by diuresis or catheter. Filling by catheter may be continuous or incremental; the precise filling rate should be stated. When the incremental method is used the volume increment should be stated. For general discussion, the following terms for the range of filling rate may be used:
    (i) up to 10 ml/min is slow-fill cystometry ('physiological' filling),
    (ii) 10–100 ml/min is medium-fill cystometry;
    (iii) over 100 ml/min is rapid-fill cystometry.

Technique

(a) Fluid-filled catheter—specify number of catheters, single or multiple lumens, type of catheter (manufacturer), size of catheter.
(b) Catheter tip transducer—list specifications.
(c) Other catheters—list specifications.
(d) Measuring equipment.

Definitions

Intravesical pressure is the pressure within the bladder.

Abdominal pressure is taken to be the pressure surrounding the bladder. In current practice it is estimated from rectal or, less commonly, extraperitoneal pressure.

Detrusor pressure is that component of intravesical pressure that is created by forces in the bladder wall (passive and active). It is estimated by subtracting abdominal pressure from intravesical pressure. The simultaneous measurement of abdominal pressure is essential for the interpretation of the intravesical pressure trace. However, artefacts on the detrusor pressure trace may be produced by intrinsic rectal contractions.

Bladder sensation is difficult to evaluate because of its subjective nature. It is usually assessed by questioning the patient in relation to the fullness of the bladder during cystometry.

Commonly used descriptive terms include:

First desire to void.

Normal desire to void (defined as the feeling that leads the patient to pass urine at the next convenient moment, but voiding can be delayed if necessary).

Strong desire to void (defined as a persistent desire to void without the fear of leakage).

Urgency (defined as a strong desire to void accompanied by fear of leakage or fear of pain).

Pain (the site and character of which should be specified). Pain during bladder filling or micturition is abnormal.

The use of objective or semi-objective tests for sensory function, such as electrical threshold studies (sensory testing), is discussed in detail in 5.5.

The term 'capacity' must be qualified.

Maximum cystometric capacity, in patients with normal sensation, is the volume at which the patient feels he/she can no longer delay micturition. In the absence of sensation the maximum cystometric capacity cannot be defined in the same terms and is the volume at which the clinician decides to terminate filling. In the presence of sphincter incompetence the maximum cystometric capacity may be significantly increased by occlusion of the urethra, e.g. by Foley catheter.

The *functional bladder capacity,* or voided volume, is more relevant and is assessed from a frequency/volume chart (urinary diary).

The *maximum (anaesthetic) bladder capacity* is the volume measured after filling during a deep general or spinal/epidural anaesthetic, specifying fluid temperature, filling pressure and filling time.

Compliance indicates the change in volume for a change in pressure. Compliance is calculated by dividing the volume change (Δ V) by the change in detrusor pressure (Δ Pdet) during that change in bladder volume (C = Δ V/Δ Pdet). Compliance is expressed as ml/cm H_2O (see 6.1.1.4).

3.2 *Urethral pressure measurement*

It should be noted that the urethral pressure and the urethral closure pressure are idealized concepts which represent the ability of the urethra to prevent leakage (see 6 1.5). In current urodynamic practice the urethral pressure is measured by a number of different techniques which do not always yield consistent values. Not only do the values differ with the method of measurement but there is often lack of consistency for a single method. For example, the effect of catheter rotation when urethral pressure is measured by a catheter-mounted transducer.

Intraluminal urethral pressure may be measured:

(a) At rest, with the bladder at any given volume.
(b) During coughing or straining.
(c) During the process of voiding (see 4.4).

Measurements may be made at one point in the urethra over a period of time, or at several points along the urethra consecutively, forming a *urethral pressure profile* (UPP).

Storage phase

Two types of UPP may be measured:

(a) Resting urethral pressure profile—with the bladder and subject at rest.
(b) Stress urethral pressure profile—with a defined applied stress (e.g. cough, strain, valsalva).

In the storage phase the *urethral pressure profile* denotes the intraluminal pressure along the length of the urethra. All systems are zeroed at atmospheric pressure. For external transducers the reference point is the superior edge of the symphysis pubis. For catheter-mounted transducers the reference point is the transducer itself. Intravesical pressure should be measured to exclude a simultaneous detrusor contraction. The subtraction of intravesical pressure from urethral pressure produces the *urethral closure pressure profile.*

The simultaneous recording of both intravesical and intra-urethral pressures is essential during stress urethral profilometry

Specify

(a) Infusion medium (liquid or gas).
(b) Rate of infusion.
(c) Stationary, continuous or intermittent withdrawal.
(d) Rate of withdrawal.
(e) Bladder volume.
(f) Position of patient (supine, sitting or standing).

Technique

(a) Open catheter—specify type (manufacturer), size, number, position and orientation of side or end hole.
(b) Catheter-mounted transducers—specify manufacturer, number of transducers, spacing of transducers along the catheter, orientation with respect to one another, transducer design, e.g. transducer face depressed or flush with catheter surface, catheter diameter and material. The orientation of the transducer(s) in the urethra should be stated.
(c) Other catheters, e.g. membrane, fibre-optic—specify type (manufacturer), size and number of channels as for micro-transducer catheter.
(d) Measurement technique—for stress profiles the particular stress employed should be stated, e.g. cough or valsalva.
(e) Recording apparatus—describe type of recording apparatus. The frequency response of the total system should be stated. The frequency response of the catheter in the perfusion method can be assessed by blocking the eyeholes and recording the consequent rate of change of pressure.

Definitions (Fig. 1: referring to profiles measured in storage phase)

Maximum urethral pressure is the maximum pressure of the measured profile.

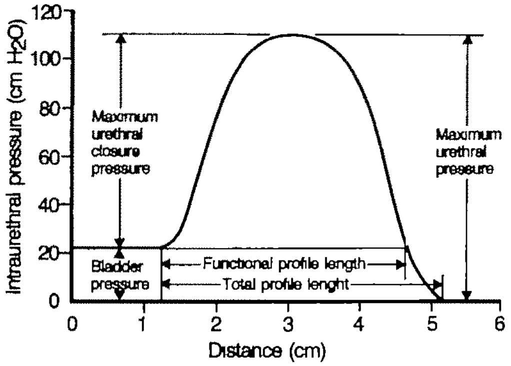

Fig. 1. Diagram of a female urethral pressure profile (static) with ICS recommended nomenclature.

Maximum urethral closure pressure is the maximum difference between the urethral pressure and the intravesical pressure.

Functional profile length is the length of the urethra along which the urethral pressure exceeds intravesical pressure.

Functional profile length (on stress) is the length over which the urethral pressure exceeds the intravesical pressure on stress.

Pressure 'transmission' ratio is the increment in urethral pressure on stress as a percentage of the simultaneously recorded increment in intravesical pressure. For stress profiles obtained during coughing, pressure transmission ratios can be obtained at any point along the urethra. If single values are given, the position in the urethra should be stated. If several pressure transmission ratios are defined at different points along the urethra, a pressure 'transmission' profile is obtained. During 'cough profiles' the amplitude of the cough should be stated if possible.

Note: the term 'transmission' is in common usage and cannot be changed. However, transmission implies a completely passive process. Such an assumption is not yet justified by scientific evidence. A role for muscular activity cannot be excluded.

Total profile length is not generally regarded as a useful parameter.

The information gained from urethral pressure measurements in the storage phase is of limited value in the assessment of voiding disorders.

3.3 *Quantification of urine loss*

Subjective grading of incontinence may not indicate reliably the degree of abnormality. However, it is important to relate the management of the individual patients to their complaints and personal circumstances, as well as to objective measurements.

To assess and compare the results of the treatment of different types of incontinence in different centres, a simple standard test can be used to measure urine loss objectively in any subject. To obtain a representative result, especially in subjects with variable or intermittent urinary incontinence, the test should occupy as long a period as possible; yet it must be practical. The circumstances should approximate to those of everyday life, yet be similar for all subjects to allow meaningful comparison. On the basis of pilot studies performed in various centres, an internal report of the ICS (fifth) recommended a test occupying a period during which a series of standard activities was carried out. This test can be extended by further 1-h periods if the result of the first 1-h test is not considered representative by either the patient or the investigator. Alternatively the test can be repeated after filling the bladder to a defined volume.

The total amount of urine lost during the test period is determined by weighing a collecting device such as a nappy, absorbent pad or condom appliance. A nappy or pad should be worn inside waterproof underpants or should have a waterproof backing. Care should be taken to use a collecting device of adequate capacity.

Immediately before the test begins, the collecting device is weighed to the nearest gram.

Typical test schedule

(a) Test is started without the patient voiding.
(b) Preweighed collecting device is put on and first 1-h test period begins.
(c) Subject drinks 500 ml sodium-free liquid within a short period (max. 15 min), then sits or rests.
(d) Over a 30-min period, subject walks, including stair-climbing equivalent to one flight up and down.
(e) During the remaining period the subject performs the following activities:
    (i) standing up from sitting, 10 times,
    (ii) coughing vigorously, 10 times,
    (iii) running on the spot for 1 min,
    (iv) bending to pick up small object from floor, 5 times,
    (v) washing hands in running water for 1 min.

(f) At the end of the 1-h test the collecting device is removed and weighed.
(g) If the test is regarded as representative the subject voids and the volume is recorded.
(h) Otherwise the test is repeated preferably without voiding.

If the collecting device becomes saturated or filled during the test it should be removed and weighed, and replaced by a fresh device. The total weight of urine lost during the test period is taken to be equal to the gain in weight of the collecting device(s). In interpreting the results of the test it should be born in mind that a weight gain of up to 1 g may be due to weighing errors, sweating or vaginal discharge.

The activity programme may be modified according to the subject's physical ability. If substantial variations from the usual test schedule occur, this should be recorded so that the same schedule can be used on subsequent occasions.

In principle the subject should not void during the test period. If the patient experiences urgency, then he/she should be persuaded to postpone voiding and to perform as many of the activities in section (e) as possible in order to detect leakage. Before voiding, the collection device is removed for weighing. If inevitable voiding cannot be postponed then the test is terminated. The voided volume and the duration of the test should be recorded. For subjects not completing the full test the results may require separate analysis, or the test may be repeated after rehydration.

The test result is given as grams urine lost in the 1-h test period in which the greatest urine loss is recorded.

Additional procedures

Additional procedures intended to give information of diagnostic value are permissible provided they do not interfere with the basic test. For example, additional changes and weighing of the collecting device can give information about the timing of urine loss. The absorbent nappy may be an electronic recording nappy so that the timing is recorded directly.

Presentation of results

Specify

(a) Collecting device.
(b) Physical condition of subject (ambulant, chairbound, bedridden).
(c) Relevant medical condition of subject.
(d) Relevant drug treatments.
(e) Test schedule.

In some situations the timing of the test (e.g. in relation to the menstrual cycle) may be relevant.

Findings

Record weight of urine lost during the test (in the case of repeated tests, greatest weight in any stated period). A loss of <1 g is within experimental error and the patients should be regarded as essentially dry. Urine loss should be measured and recorded in grams.

Statistics

When performing statistical analysis of urine loss in a group of subjects, non-parametric statistics should be employed, since the values are not normally distributed.

4. Procedures related to the evaluation of micturition

4.1 *Urine flow rate measurement*

Urinary flow may be described in terms of *rate* and *pattern* and may be *continuous* or *intermittent*. *Flow rate* is defined as the volume of fluid expelled via the urethra per unit time. It is expressed in ml/s.

Specify

(a) Voided volume.
(b) Patient environment and position (supine, sitting or standing).
(c) Filling:
  (i) by diuresis (spontaneous or forced: specify regimen),
  (ii) by catheter (transurethral or suprapubic).
(d) Type of fluid.

Technique

(a) Measuring equipment.
(b) Solitary procedure or combined with other measurements.

Definitions

(a) *Continuous flow* (Fig. 2)

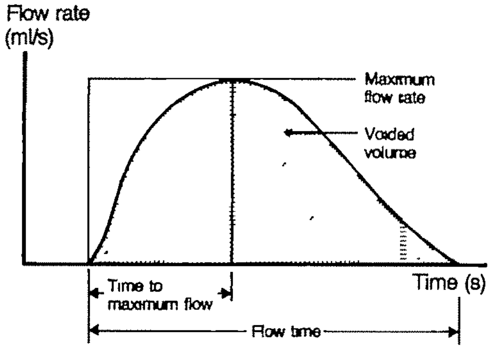

Fig. 2. Diagram of a continuous urine flow recording with ICS recommended nomenclature

Voided volume is the total volume expelled via the urethra.

Maximum flow rate is the maximum measured value of the flow rate.

Averge flow rate is voided volume divided by flow time. The calculation of average flow rate is only meaningful if flow is continuous and without terminal dribbling.

Flow time is the time over which measurable flow actually occurs.

Time to maximum flow is the elapsed time from onset of flow to maximum flow.

The flow pattern must be described when flow time and average flow rate are measured.

(b) *Intermittent flow* (Fig. 3)

The same parameters used to characterize continuous flow may be applicable if care is exercised in patients with intermittent flow. In measuring flow time the time intervals between flow episodes are disregarded.

Voiding time is total duration of micturition, i.e. includes interruptions. When voiding is completed without interruption, voiding time is equal to flow time.

4.2 *Bladder pressure measurement during micturition*

The specifications of patient position, access for pressure measurement, catheter type and measuring equipment are as for cystometry (see 3.1).

Definitions (Fig. 4)

Opening time is the elapsed time from initial rise in detrusor pressure to onset of flow. This is the initial isovolumetric contraction period of micturition. Time lags should be taken into account. In most urodynamic systems a time lag occurs equal to the time taken for the urine to pass from the point of pressure measurement to the uroflow transducer.

The following parameters are applicable to measurements of each of the pressure curves: intravesical, abdominal and detrusor pressure.

Premicturition pressure is the pressure recorded immediately before the initial isovolumetric contraction.

Opening pressure is the pressure recorded at the onset of measured flow.

Maximum pressure is the maximum value of the measured pressure.

Pressure at maximum flow is the pressure recorded at maximum measured flow rate.

Contraction pressure at maximum flow is the difference between pressure at maximum flow and premicturition pressure.

Postmicturition events (e.g. after contraction) are not well understood and so cannot be defined as yet.

4.3 *Pressure flow relations*

In the early days of urodynamics the flow rate and voiding pressure were related as a 'urethral resistance factor'. The concept of a resistance factor originates from rigid tube hydrodynamics. The urethra does not generally behave as a rigid tube as it is an irregular and distensible conduit whose walls and surroundings have active and passive elements and hence influence the flow through it. Therefore a resistance factor cannot provide a valid comparison between patients.

There are many ways of displaying the relations between flow and pressure during micturition; an example is suggested in the ICS Third Report (Bates *et al.* 1980) (Fig. 5). As yet, available data do not permit a standard presentation of pressure/flow parameters.

When data from a group of patients are pre-

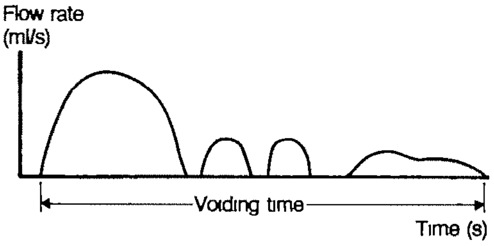

Fig. 3. Diagram of an interrupted urine flow recording with ICS recommended nomenclature.

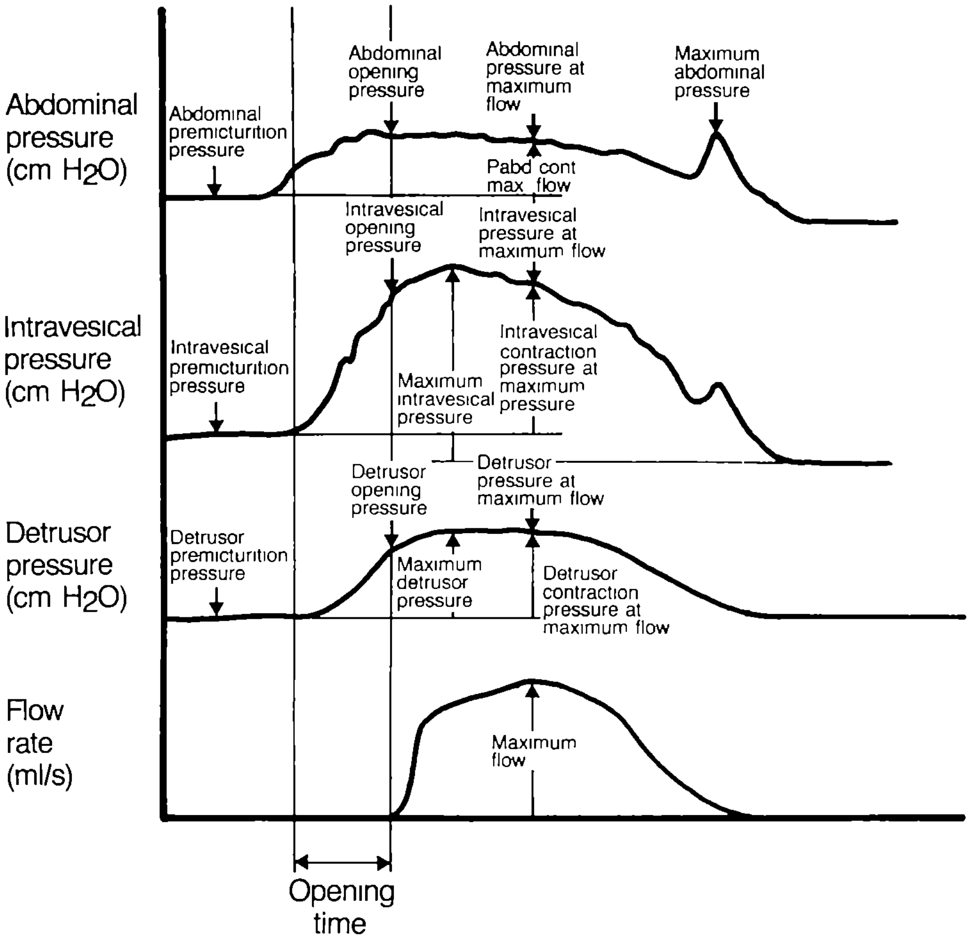
Abdominal pressure (cm H2O)
Intravesical pressure (cm H2O)
Detrusor pressure (cm H2O)
Flow rate (ml/s)
Abdominal premicturition pressure
Abdominal opening pressure
Abdominal pressure at maximum flow
Maximum abdominal pressure
Pabd cont max flow
Intravesical opening pressure
Intravesical pressure at maximum flow
Intravesical premicturition pressure
Maximum intravesical pressure
Intravesical contraction pressure at maximum pressure
Detrusor opening pressure
Detrusor pressure at maximum flow
Detrusor premicturition pressure
Maximum detrusor pressure
Detrusor contraction pressure at maximum flow
Maximum flow
Opening time

Fig. 4. Diagram of a pressure-flow recording of micturition with ICS recommended nomenclature.

sented, pressure-flow relations may be shown on a graph as illustrated in Fig. 5. This form of presentation allows lines of demarcation to be drawn on the graph to separate the results according to the problem being studied. The points shown in Fig. 5 are purely illustrative to indicate how the data might fall into groups. The group of equivocal results might include either an unrepresentative micturition in an obstructed or an unobstructed patient, or underactive detrusor function with or without obstruction. This is the group which invalidates the use of 'urethral resistance factors'.

4.4 *Urethral pressure measurements during voiding (VUPP)*

The VUPP is used to determine the pressure and site of urethral obstruction.

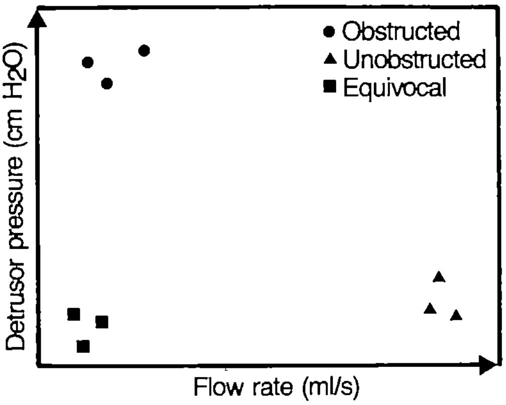

Fig. 5. Diagram illustrating the presentation of pressure flow data on individual patients in three groups of three patients· obstructed, equivocal and unobstructed

Pressure is recorded in the urethra during voiding. The technique is similar to that used in the UPP measured during storage (the resting and stress profiles 3.2).

Specify as for UPP during storage (3.2).

Accurate interpretation of the VUPP depends on the simultaneous measurement of intravesical pressure and the measurement of pressure at a precisely localized point in the urethra. Localization may be achieved by a radio-opaque marker on the catheter which allows the pressure measurements to be related to a recognizable point in the urethra.

This technique is not fully developed, and a number of technical as well as clinical problems need to be solved before the VUPP is widely used.

4.5 *Residual urine measurement*

Residual urine is defined as the volume of fluid remaining in the bladder immediately after the completion of micturition. The measurement of residual urine forms an integral part of the study of micturition. However, voiding in unfamiliar surroundings may lead to unrepresentative results, as may voiding on command with a partially filled or overfilled bladder. Residual urine is commonly estimated by the following methods:

(a) Catheter or cystoscope (transurethral, suprapubic).
(b) Radiography (excretion urography, micturition cystography).
(c) Ultrasonics.
(d) Radioisotopes (clearance, gamma camera).

When estimating residual urine the measurement of voided volume and the time interval between voiding and residual urine estimation should be recorded: this is particularly important if the patient is in a diuretic phase. In the condition of vesicoureteric reflux, urine may re-enter the bladder after micturition and may falsely be interpreted as residual urine. The presence of urine in bladder diverticula following micturition presents special problems of interpretation, since a diverticulum may be regarded either as part of the bladder cavity or as outside the functioning bladder.

The various methods of measurement each have limitations as to their applicability and accuracy in the various conditions associated with residual urine. Therefore it is necessary to choose a method appropriate to the clinical problems. The absence of residual urine is usually an observation of clinical value, but does not exclude infravesical obstruction or bladder dysfunction. An isolated finding of residual urine requires confirmation before being considered significant.

5. Procedures related to neurophysiological investigations of the urinary tract during filling and voiding

5.1 *Electromyography*

Electromyography (EMG) is the study of electrical potentials generated by the depolarization of muscle. The following refers to striated muscle EMG. The functional unit in EMG is the motor unit. This is comprised of a single motor neurone and the muscle fibres it innervates. A motor unit action potential is the recorded depolarization of muscle fibres which results from activation of a single anterior horn cell. Muscle action potentials may be detected either by needle electrodes, or by surface electrodes.

Needle electrodes are placed directly into the muscle mass and permit visualization of the individual motor unit action potentials.

Surface electrodes are applied to an epithelial surface as close to the muscle under study as possible. Surface electrodes detect the action potentials from groups of adjacent motor units underlying the recording surface.

EMG potentials may be displayed on an oscilloscope screen or played through audio amplifiers. A permanent record of EMG potentials can only be made using a chart recorder with a high-frequency response (in the range of 10 kHz).

EMG should be interpreted in the light of the patients symptoms, physical findings and urological and urodynamic investigations.

General information

Specify

(a) EMG (solitary procedure, part of urodynamic or other electrophysiological investigation).
(b) Patient position (supine, standing, sitting or other).
(c) Electrode placement:
    (i) Sampling site (intrinsic striated muscle of the urethra, peri-urethral striated

muscle, bulbocavernosus muscle, external anal sphincter, pubococcygeus or other). State whether sites are single or multiple, unilateral or bilateral. Also state number of samples per site.
   (ii) Recording electrode. Define the precise anatomical location of the electrode. For needle electrodes, include site of needle entry, angle of entry and needle depth. For vaginal or urethral surface electrodes state method of determining position of electrode.
   (iii) Reference electrode position.

Note: ensure that there is no electrical interference with any other machines, e.g. X-ray apparatus.

Technical information

Specify

(a) Electrodes
   (i) Needle electrodes
      —design (concentric, bipolar, monopolar, single fibre, other),
      —dimensions (length, diameter, recording area),
      —electrode material (e.g. platinum).
   (ii) Surface electrodes
      —type (skin, plug, catheter, other),
      —size and shape,
      —electrode material,
      —mode of fixation to recording surface,
      —conducting medium (e.g. saline, jelly).

(b) Amplifier (make and specifications).

(c) Signal processing (data: raw, averaged, integrated or other).

(d) Display equipment (make and specifications to include method of calibration, time base, full scale deflection in microvolts and polarity).
   (i) Oscilloscope.
   (ii) Chart recorder.
   (iii) Loudspeaker.
   (iv) Other.

(e) Storage (make and specifications)
   (i) Paper.
   (ii) Magnetic tape recorder.
   (iii) Microprocessor.
   (iv) Other.

(f) Hard copy production (make and specifications)
   (i) Chart recorder.
   (ii) Photographic/video reproduction of oscilloscope screen.
   (iii) Other.

EMG findings

(a) Individual motor unit action potentials. Normal motor unit potentials have a characteristic configuration, amplitude and duration. Abnormalities of the motor unit may include an increase in the amplitude, duration and complexity of waveform (polyphasicity) of the potentials. A polyphasic potential is defined as one having more than five deflections. The EMG findings of fibrillations, positive sharp waves and bizarre high-frequency potentials are thought to be abnormal.

(b) Recruitment patterns. In normal subjects there is a gradual increase in 'pelvic floor' and 'sphincter' EMG activity during bladder filling. At the onset of micturition there is complete absence of activity. Any sphincter EMG activity during voiding is abnormal unless the patient is attempting to inhibit micturition. The finding of increased sphincter EMG activity, during voiding, accompanied by characteristics simultaneous detrusor pressure and flow changes is described by the term, detrusor-sphincter-dyssynergia. In this condition a detrusor contraction occurs concurrently with an inappropriate contraction of the urethral and or periurethral striated muscle.

5.2 *Nerve conduction studies*

Nerve conduction studies involve stimulation of a peripheral nerve, and recording the time taken for a response to occur in muscle, innervated by the nerve under study. The time taken from stimulation of the nerve to the response in the muscle is called the 'latency'. Motor latency is the time taken by the fastest motor fibres in the nerve to conduct impulses to the muscle and depends on conduction distance and the conduction velocity of the fastest fibres.

General information (also applicable to reflex latencies and evoked potentials—see below)

Specify

(a) Type of investigation
   (i) Nerve conduction study (e.g. pudendal nerve).
   (ii) Reflex latency determination (e.g. bulbocavernosus).

- (iii) Spinal evoked potential.
- (iv) Cortical evoked potential.
- (v) Other.

(b) Is the study a solitary procedure or part of urodynamic or neurophysiological investigations?

(c) Patient position and environmental temperature, noise level and illumination.

(d) Electrode placement. Define electrode placement in precise anatomical terms. The exact interelectrode distance is required for nerve conduction velocity calculations.
- (i) Stimulation site (penis, clitoris, urethra, bladder neck, bladder or other).
- (ii) Recording sites (external anal sphincter, peri-urethral striated muscle, bulbocavernosus muscle, spinal cord, cerebral cortex or other). When recording spinal evoked responses, the sites of the recording electrodes should be specified according to the bony landmarks (e.g. L4). In cortical evoked responses the sites of the recording electrodes should be specified as in the International 10–20 system (Jasper 1958). The sampling techniques should be specified (single or multiple, unilateral or bilateral, ipsilateral or contralateral or other).
- (iii) Reference electrode position.
- (iv) Grounding electrode 'site': ideally this should be between the stimulation and recording sites to reduce stimulus artefact.

Technical information (also applicable to reflex latencies and evoked potential—see below)

Specify

(a) Electrodes (make and specifications; describe separately stimulus and recording electrodes as below)
- (i) Design (e.g. needle, plate, ring and configuration of anode and cathode where applicable).
- (ii) Dimensions.
- (iii) Electrode material (e.g. platinum).
- (iv) Contact medium.

(b) Stimulator (make and specifications)
- (i) Stimulus parameters (pulse width, frequency, pattern, current density, electrode impedance in Kohms. Also define in terms of threshold, e.g. in case of supramaximal stimulation).

(c) Amplifier (make and specifications)
- (i) Sensitivity (mV–μV).
- (ii) Filters—low pass (Hz) or high pass (kHz).
- (iii) Sampling time (ms).

(d) Averager (make and specifications)
- (i) Number of stimuli sampled.

(e) Display equipment (make and specifications to include method of calibration, time base, full scale deflection in microvolts and polarity)
- (i) Oscilloscope.

(f) Storage (make and specifications)
- (i) Paper.
- (ii) Magnetic tape recorder.
- (iii) Microprocessor.
- (iv) Other.

(g) Hard copy production (make and specification)
- (i) Chart recorder.
- (ii) Photographic/Video reproduction of oscilloscope screen.
- (iii) XY recorder.
- (iv) Other.

Description of nerve conduction studies

Recordings are made from muscle, and the latency of response of the muscle is measured. The latency is taken as the time to onset, of the earliest reponse.

(a) To ensure that response time can be measured precisely, the gain should be increased to give a clearly defined take-off point. (Gain setting at least 100 μV/div and using a short time base, e.g 1–2 ms/div).

(b) Additional information may be obtained from nerve conduction studies, if, when using surface electrodes to record a compound muscle action potential, the amplitude is measured. The gain setting must be reduced so that the whole response is displayed and a longer time base is recommended (e.g. 1 mV/div and 5 ms/div). Since the amplitude is proportional to the number of motor unit potentials within the vicinity of the recording electrodes, a reduction in amplitude indicates loss of motor units and therefore denervation. (Note: A prolongation of latency is not necessarily indicative of denervation.)

5.3 *Reflex latencies*

Reflex latencies require stimulation of sensory fields and recordings from the muscle which contracts reflexly in response to the stimulation. Such responses are a test of reflex arcs which are comprised of both afferent and efferent limbs and a synaptic region within the central nervous system. The reflex latency expresses the nerve conduction velocity in both limbs of the arc and the integrity of the central nervous system at the level of the synapse(s). Increased reflex latency may occur as a result of slowed afferent or efferent nerve conduction or due to central nervous system conduction delays.

General information and *technical information.* The same technical and general details apply as discussed above under nerve conduction studies (5.2).

Description of reflex latency measurements

Recordings are made from muscle, and the latency of response of the muscle is measured. The latency is taken as the time to onset, of the earliest response.

To ensure that response time can be measured precisely, the gain should be increased to give a clearly defined take-off point. (Gain setting at least 100 μV/div and using a short time base, e.g. 1–2 ms/div.)

5.4 *Evoked responses*

Evoked responses are potential changes in central nervous system neurones resulting from distant stimulation, usually electrical. They are recorded using averaging techniques. Evoked responses may be used to test the integrity of peripheral, spinal and central nervous pathways. As with nerve conduction studies, the conduction time (latency) may be measured. In addition, information may be gained from the amplitude and configuration of these responses.

General information and *technical information.* See above under *Nerve conduction studies* (5.2).

Description of evoked responses

Describe the presence or absence of stimulus evoked responses and their configuration.

Specify

(a) Single or multiphasic response.

(b) Onset of response: defined as the start of the first reproducible potential. Since the onset of the response may be difficult to ascertain precisely, the criteria used should be stated.

(c) Latency to onset: defined as the time (ms) from the onset of stimulus to the onset of response. The central conduction time relates to cortical-evoked potentials and is defined as the difference between the latencies of the cortical- and the spinal-evoked potentials. This parameter may be used to test the integrity of the corticospinal neuraxis.

(d) Latencies to peaks of positive and negative deflections in multiphasic responses (Fig. 6). P denotes positive deflections, N denotes negative deflections. In multiphasic responses, the peaks are numbered consecutively (e.g. P1, N1, P2, N2 . . .) or according to the latencies to peaks in milliseconds (e.g. P44, N52, P66 . . .)

(e) The amplitude of the responses is measured in μV.

5.5 *Sensory testing*

Limited information, of a subjective nature, may be obtained during cystometry by recording such parameters as the first desire to micturate, urgency or pain. However, sensory function in the lower urinary tract can be assessed by semi-objective tests by the measurement of urethral and/or vesical sensory thresholds to a standard applied stimulus such as a known electrical current.

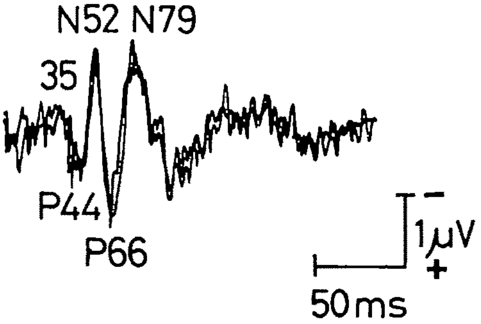

Fig. 6. Multiphasic evoked response recorded from the cerebral cortex after stimulation of the dorsal aspect of the penis The recording shows the conventional labelling of negative (N) and positive (P) deflections with the latency of each deflection from the point of stimulation in milliseconds

General information

Specify

(a) Patient's position (supine, sitting, standing, other).
(b) Bladder volume at time of testing.
(c) Site of applied stimulus (intravesical, intra-urethral).
(d) Number of times the stimulus was applied and the response recorded. Define the sensation recorded, e.g. the first sensation or the sensation of pulsing.
(e) Type of applied stimulus
  (i) Electrical current: it is usual to use a constant current stimulator in urethral sensory measurement
  —state electrode characteristics and placement as in section on EMG,
  —state electrode contact area and distance between electrodes if applicable,
  —state impedance characteristics of the system,
  —state type of conductive medium used for electrode/epithelial contact (*note: topical anaesthetic agents should not be used*),
  —state stimulator make and specifications,
  —state stimulation parameters (pulse width, frequency, pattern, duration, current density).
  (ii) Other—e.g. mechanical, chemical.

Definition of sensory thresholds

The vesical/urethral sensory threshold is defined as the least current which consistently produces a sensation perceived by the subject during stimulation at the site under investigation. However, the absolute values will vary in relation to the site of the stimulus, the characteristics of the equipment and the stimulation parameters. Normal values should be established for each system.

6. A classification of lower urinary tract dysfunction

The lower urinary tract is composed of the *bladder* and *urethra*. They form a functional unit and their interaction cannot be ignored. Each has two functions: the bladder to store and void, the urethra to control and convey. When a reference is made to the hydrodynamic function or to the whole anatomical unit as a storage organ—the vesica urinaria—the correct term is the *bladder*. When the smooth muscle structure known as the m.detrusor urinae is being discussed then the correct term is *detrusor*. For simplicity the bladder/detrusor and the urethra will be considered separately so that a classification based on a combination of functional anomalies can be reached. Sensation cannot be precisely evaluated but must be assessed. This classification depends on the results of various objective urodynamic investigations. A complete urodynamic assessment is not necessary in all patients. However, studies of the filling and voiding phases are essential for each patient. As the bladder and urethra may behave differently during the storage and micturition phases of bladder function, it is most useful to examine bladder and urethral activity separately in each phase.

Terms used should be objective, definable, and ideally should be applicable to the whole range of abnormality. When authors disagree with the classification presented below, or use terms which have not been defined here, their meaning should be made clear.

Assuming the absence of inflammation, infection and neoplasm, *lower urinary tract dysfunction* may be caused by:

(a) Disturbance of the pertinent nervous or psychological control system.
(b) Disorders of muscle function.
(c) Structural abnormalities.

Urodynamic diagnoses based on this classification should correlate with the patient's symptoms and signs. For example, the presence of an unstable contraction in an asymptomatic continent patient does not warrant a diagnosis of detrusor overactivity during storage

6.1 *The storage phase*

6.1.1. *Bladder function during storage*
This may be described according to:
6.1.1.1 Detrusor activity.
6.1.1.2 Bladder sensation.
6.1.1.3 Bladder capacity.
6.1.1.4 Compliance.

6.1.1.1 *Detrusor activity.* In this context detrusor activity is interpreted from the measurement of detrusor pressure (pdet).
Detrusor activity may be:
(a) Normal.
(b) Overactive.

(a) *Normal detrusor function*

During the filling phase the bladder volume increases without a significant rise in pressure (accommodation). No involuntary contractions occur despite provocation.

A normal detrusor so defined may be described as 'stable'.

(b) *Overactive detrusor function*

Overactive detrusor function is characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked and which the patient cannot completely suppress. Involuntary detrusor contractions may be provoked by rapid filling, alterations of posture, coughing, walking, jumping and other triggering procedures. Various terms have been used to describe these features and they are defined as follows.

The *unstable detrusor* is one that is shown objectively to contract, spontaneously or on provocation, during the filling phase while the patient is attempting to inhibit micturition. Unstable detrusor contractions may be asymptomatic or may be interpreted as a normal desire to void. The presence of these contractions does not necessarily imply a neurological disorder. Unstable contractions are usually phasic in type (Fig. 7a). A gradual increase in detrusor pressure without subsequent decrease is best regarded as a change of compliance (Fig 7b).

Detrusor hyper-reflexia is defined as overactivity due to disturbance of the nervous control mechanisms. The term detrusor hyper-reflexia should only be used when there is objective evidence of a relevant neurological disorder. The use of conceptual and undefined terms such as hypertonic, systolic, uninhibited, spastic and automatic should be avoided.

6.1.1.2 *Bladder sensation.* Bladder sensation during filling can be classified in qualitative terms (see 3.1) and by objective measurement (see 5.5). Sensation can be classified broadly as follows:

(a) Normal.
(b) Increased (hypersensitive).
(c) Reduced (hyposensitive).
(d) Absent.

6.1.1.3 *Bladder capacity.* (see 3.1).

6.1.1.4 *Compliance.* This is defined as $\Delta V/\Delta p$ (see 3.1).

Compliance may change during the cystometric examination and is variably dependent upon a number of factors including:

(a) Rate of filling.
(b) The part of the cystometrogram curve used for compliance calculation.
(c) The volume interval over which compliance is calculated.
(d) The geometry (shape) of the bladder.
(e) The thickness of the bladder wall.
(f) The mechanical properties of the bladder wall.
(g) The contractile/relaxant properties of the detrusor.

During normal bladder filling little or no pressure change occurs and this is termed 'normal compliance'. However, at the present time there are insufficient data to define normal, high and low compliance.

When reporting compliance, specify:

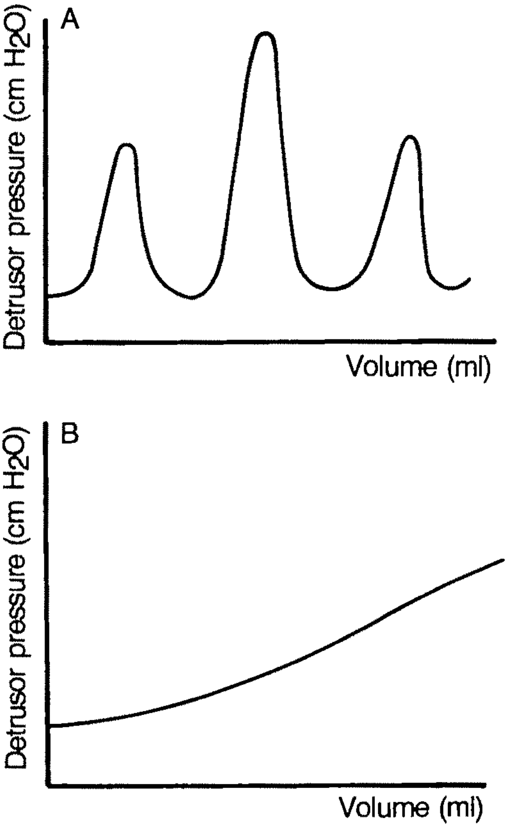

Fig. 7. Diagrams of filling cystometry to illustrate (A) typical phasic unstable detrusor contraction; (B) the gradual increase of detrusor pressure with filling characteristic of reduced bladder compliance.

(a) The rate of bladder filling.
(b) The bladder volume at which compliance is calculated.
(c) The volume increment over which compliance is calculated.
(d) The part of the cystometrogram curve used for the calculation of compliance.

6.1.2 *Urethral function during storage*

The urethral closure mechanism during storage may be:
(a) Normal.
(b) Incompetent.

(a) The *normal urethral closure mechanism* maintains a positive urethral closure pressure during filling even in the presence of increased abdominal pressure. Immediately before micturition the normal closure pressure decreases to allow flow.

(b) An *incompetent urethral closure mechanism* is defined as one which allows leakage of urine in the absence of a detrusor contraction. Leakage may occur whenever intravesical pressure exceeds intra-urethral pressure (genuine stress incontinence) or when there is an involuntary fall in urethral pressure. Terms such as 'the unstable urethra' await further data and precise definition.

6.1.3 *Urinary incontinence*

Urinary incontinence is involuntary loss of urine which is objectively demonstrable and a social or hygienic problem. Loss of urine through channels other than the urethra is extra-urethral incontinence.

Urinary incontinence denotes:
(a) A symptom.
(b) A sign.
(c) A condition.

The symptom indicates the patient's statement of involuntary urine loss.

The sign is the objective demonstration of urine loss.

The condition is the urodynamic demonstration of urine loss.

Symptoms

Urge incontinence is the involuntary loss of urine associated with a strong desire to void (urgency). *Urgency* may be associated with two types of dysfunction:
(a) Overactive detrusor function (*motor urgency*).
(b) Hypersensitivity (*sensory urgency*).

Stress incontinence indicates the patient's statement of involuntary loss of urine during physical exertion.

'Unconscious' incontinence may occur in the absence of urge and without conscious recognition of the urinary loss.

Enuresis means any involuntary loss of urine. If it is used to denote incontinence during sleep, it should always be qualified with the adjective 'nocturnal'.

Post micturition dribble and *continuous leakage* denote other symptomatic forms of incontinence.

Signs

The sign of stress incontinence denotes the observation of loss of urine from the urethra synchronous with physical exertion (e.g. coughing). Incontinence may also be observed without physical exercise. Post micturition dribble and continuous leakage denote other signs of incontinence. Symptoms and signs alone may not disclose the cause of urinary incontinence. Accurate diagnosis often requires urodynamic investigation in addition to careful history and physical examination.

Conditions

Genuine stress incontinence is the involuntary loss of urine occurring when, in the absence of a detrusor contraction, the intravesical pressure exceeds the maximum urethral pressure.

Reflex incontinence is loss of urine due to detrusor hyper-reflexia and/or involuntary urethral relaxation in the absence of the sensation usually associated with the desire to micturate. This condition is only seen in patients with neuropathic bladder/urethral disorders.

Overflow incontinence is any involuntary loss of urine associated with over distension of the bladder.

6.2 *The voiding phase*

6.2.1 *The detrusor during voiding*

During micturition the detrusor may be:

(a) Acontractile.
(b) Underactive.
(c) Normal.

(a) The *acontractile detrusor*. This is a detrusor that cannot be demonstrated to contract during urodynamic studies. *Detrusor areflexia* is defined as acontractility due to an abnormality of nervous control and denotes the complete absence of centrally co-ordinated contraction. In detrusor areflexia due to a lesion of the conus medullaris or sacral nerve outflow, the detrusor should be described as *decentralized,* not denervated, since the peripheral neurones remain. In such bladders pressure fluctuations of low amplitude, sometimes known as 'autonomous' waves, may occasionally occur. The use of terms such as atonic, hypotonic, autonomic and flaccid should be avoided.

(b) *Detrusor underactivity.* This term should be reserved to describe detrusor activity during micturition. Detrusor underactivity is defined as a detrusor contraction of inadequate magnitude and/or duration to effect bladder emptying with a normal time span. Patients may have underactivity during micturition and detrusor overactivity during filling.

(c) *Normal detrusor contractility.* Normal voiding is achieved by a voluntary initiated detrusor contraction that is sustained and can usually be suppressed voluntarily. A normal detrusor contraction will effect complete bladder emptying in the absence of obstruction. For a given detrusor contraction, the magnitude of the recorded pressure rise will depend on the degree of outlet resistance.

Table 1. Principal SI units in urodynamics

Quantity	Acceptable unit	Symbol
Volume	Millilitre	ml
Time	Second	s
Flow rate	Millilitre/second	ml s^{-1}
Pressure	Centimetres of water*	cm H_2O
Length	Metres or submultiples	m, cm, mm
Velocity	Metres/second or submultiples	m s^{-1}, cm s^{-1}
Temperature	Degrees celsius	°C

* The SI unit is the pascal (Pa), but it is only practical at present to calibrate our instruments in cm H_2O. One centimetre of water pressure is approximately equal to 100 pascals (1 cm H_2O = 98·07 PA = 0·098 kPa)

6.2.2 *Urethral function during micturition*

During voiding urethral function may be:
(a) Normal.
(b) Obstructive
—overactivity,
—mechanical.

(a) The *normal urethra* opens to allow the bladder to be emptied.

(b) *Obstruction due to urethral overactivity* occurs when the urethral closure mechanism contracts against a detrusor contraction or fails to open at attempted micturition. Synchronous detrusor and urethral contraction is *detrusor/urethral dyssynergia.* This diagnosis should be qualified by stating the location and type of the urethral muscles (striated or smooth) which are involved. Despite the confusion surrounding 'sphincter' terminology, the use of certain terms is so widespread that they are retained and defined here. The terms *detrusor/external sphincter dyssynergia* or *detrusor-sphincter-dyssynergia* (DSD) describe a detrusor contraction concurrent with an involuntary contraction of the urethral and/or peri-urethral striated muscle. In the adult, detrusor sphincter dyssynergia is a feature of neurological voiding disorders. In the absence of neurological features the validity of this diagnosis should be questioned. The term *detrusor/bladder neck dyssynergia* is used to denote a detrusor contraction concurrent with an objectively demonstrated failure of bladder neck opening. No parallel term has been elaborated for possible detrusor/distal urethral (smooth muscle) dyssynergia.

Table 2. List of symbols

Basic symbols		Urological qualifiers		Value	
Pressure	p	Bladder	ves	Maximum	max
Volume	V	Urethra	ura	Minimum	min
Flow rate	Q	Ureter	ure	Average	ave
Velocity	v	Detrusor	det	Isovolumetric	isv
Time	t	Abdomen	abd	Isotonic	ist
Temperature	T	External stream	ext	Isobaric	isb
Length	l			Isometric	ism
Area	A				
Diameter	d				
Force	F				
Energy	E				
Power	P				
Compliance	C				
Work	W				
Energy/unit volume	e				

Examples:
pdet,max = maximum detrusor pressure.
e ext = kinetic energy/unit volume in the external stream

Overactivity of the striated urethral sphincter may occur in the absence of detrusor contraction, and may prevent voiding. This is not detrusor/sphincter dyssynergia.

Overactivity of the urethral sphincter may occur during voiding in the absence of neurological disease and is termed *dysfunctional voiding*. The use of terms such as 'non-neurogenic' or 'occult neuropathic' should be avoided.

Mechanical obstruction is most commonly anatomical, e.g. urethral stricture.

By using the characteristics of detrusor and urethral function during storage and micturition, an accurate definition of lower urinary tract behaviour in each patient becomes possible.

7. Units of measurement and symbols

In the urodynamic literature, pressure is measured in cm H_2O and *not* in mmHg. When Laplace's law is used to calculate tension in the bladder wall, it is often found that pressure is then measured in dyne cm^{-2}. This lack of uniformity in the systems used leads to confusion when other parameters, which are a function of pressure, are computed, for instance, 'compliance', contraction force, velocity, etc. From these few examples it is evident that standardization is essential for meaningful communication. Many journals now require that the results be given in SI units. This section is designed to give guidance in the application of the SI system to urodynamics and defines the units involved. The principal units to be used are listed in Table 1.

Symbols

It is often helpful to use symbols in a communication. The system in Table 2 has been devised to standardize a code of symbols for use in urodynamics. The rationale of the system is to have a basic symbol representing the physical quantity with qualifying subscripts. The list of basic symbols largely conforms to international usage, The qualifying subscripts relate to the basic symbols for commonly used urodynamic parameters.

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